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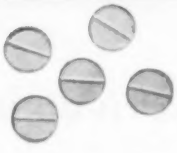

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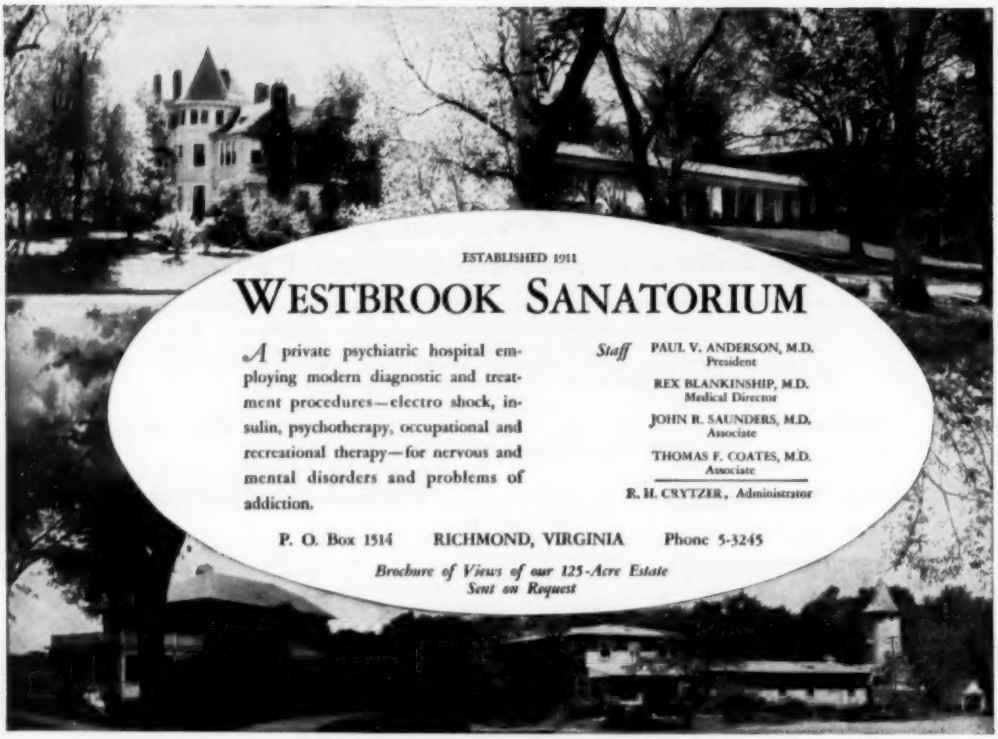

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# HISTOPATHOLOGICAL CHANGES IN THE BRAIN IN SCHIZOPHRENIA

## A Critical Review

MORTON R. WEINSTEIN, A.B.
NEW YORK

### I. INTRODUCTION

INVESTIGATIONS into a possibly characteristic histopathology of the brain in schizophrenia and other so-called functional psychoses can be considered to have begun with the pioneer researches of Alzheimer and other German workers shortly before the close of the 19th century. In the five ensuing decades some of the ablest workers in psychiatry and neuropathology have concerned themselves with this important problem. In this paper it is my purpose to describe and scrutinize the reports concerning the histopathology of schizophrenia, to examine these reports in terms of their experimental and statistical validity, and to emphasize those findings which best stand the test of such scrutiny. It is perhaps unnecessary to remark that while this undertaking is approached with humility, it is not permissible to allow one's respect for the names of pioneer workers to dull the edge of critical evaluation of their work and their interpretations. With this in mind it would be wise to begin with a consideration of the experimental and rational difficulties which beset investigators in this field and which have often in the past been too lightly appreciated or entirely ignored.

There is little doubt that the greatest difficulties in investigations of the histopathological changes in schizophrenia are encountered in the problem of establishing the limits of normal variation in the manifestations described and in the parallel problem of separating lesions associated with concurrent diseases from those, if any, characteristic of schizophrenia. None of the pathological changes to be described here are in themselves unique in the brains of schizophrenic patients; all are found to some degree in one or a variety of other disease states, visceral or neural or both. The influence of concurrent diseases on the specimens examined must be carefully determined, particularly as regards chronic somatic affections and the changes characteristic of age and senility. The terminal event in necropsy studies is of great significance to the findings reported in such material, and the effects of the mental state before death, as reflected in malnutrition, exhaustion, and trauma, must be determined, especially in material from long-institutionalized patients. The question of controls in these studies is, likewise, of importance and considerable difficulty, for similar care must be exercised to evaluate the effects of age and disease on control material. It is obvious that, with a few well-marked exceptions, findings reported without reference to adequate control material cannot be accepted, and yet the difficulty encountered in evaluating and accounting for the complications outlined here is apparently so great that many reports have appeared which in whole or in part ignored them.

Histopathological techniques as applied to nerve tissue are at best complex and prone to give variable results in the hands of different workers. Comparison of results obtained with a variety of methods, especially when those methods are not specified, is a constant source of confusion. Postmortem changes are rapid and severe in nerve tissue; reports dealing with necropsy studies which do not specify the time after death at which the material was removed and fixed add confusion and lead to misinterpretation. Recently some workers have reported on biopsy material removed during lobotomy and gyrectomy procedures, and, while this technique certainly represents an improvement over necropsy studies, the results thus obtained can be compared with the findings of the older studies only with the greatest care and with a full understanding of the techniques used in both cases. Such information is frequently omitted from published reports. Elaborate descriptions of lesions have appeared in the work of competent investigators which have subsequently been shown to be artifacts of the histological methods employed. For example, Buscaino[1] in 1920 reported finding "grape-like" accumulations of lipid material in the brains of schizophrenics, which Ferraro subsequently showed to be artifacts of alcoholic fixation, present in normal brains thus treated (Freeman, 1928[2]). Such misinterpretations might be reduced with attention to adequate control material. It must be borne in mind that in our present state of ignorance concerning the finer brain functions, which are apparently disturbed in schizophrenia, speculations regarding the functional reflections of bona fide brain lesions must be entertained with great caution. The demonstration of such lesions does not per se make schizophrenia an organic psychosis. Such a conclusion will be justifiable only when we have strong proof that the manifestations seen in the clinical picture of the disease are related as effect and cause to the lesions described, and we are still far from that level of understanding. On the other hand, it is wise to bear in mind that the failure to demonstrate pathological changes in the brain which are incontestably characteristic of schizophrenia does not stand as evidence that this affection has no organic basis, for such demonstrations may in fact wait only upon the development of suitable technical methods. Finally, there is much to be said for Spielmeyer's suggestion that the brain lesions described in association with schizophrenia may not be the cerebral manifestations of schizophrenia itself but, rather, items in the limited repertoire of cerebral response to a variety of insults; and thus schizophrenia may in reality be not one but many diseases manifesting a small number of pathological and clinical findings.[3]

## II. HISTOPATHOLOGICAL FINDINGS

1. Changes in the neural cells and nerve fibers
2. Changes in the oligodendroglial, astrocytic, and microglial elements
3. Lipid changes
4. Changes in the vascular and perivascular structures
5. The work of Papez, and Papez and Bateman

1. *Changes in the Neural Cells and Nerve Fibers.*—Among the most frequently described brain changes in schizophrenia are those involving the cortical neurons and their fibers. Rupp and Wilson in 1949,[4] in a discussion of the findings in 20 cases of schizophrenia of all types, referred to a "dropping out of cortical neuronal elements," without discussing this cell loss quantitatively or topographically. Their

material was obtained post mortem from patients who had been mentally ill for less than two years. Thirty-six of the 37 cases in the series had cardiorenal disease, and 7 had congenital cardiovascular anomalies. It should be noted here, as in many of the sections to follow, that the authors did not describe their control measures or histological methods or specify the time post mortem at which the material was taken. In 1944 Kirschbaum and Heilbrunn [5] reported on a series of 11 biopsy specimens removed from schizophrenics during lobotomy procedures. These subjects were between 25 and 50 years old, and the average duration of their mental affection had been 14.7 years. None showed evidence of physical disease. Control material consisted of brain sections from supposedly healthy people killed suddenly in accidents, and the effect of the ether anesthesia used in the lobotomies was controlled by comparison with brains from normals dying during surgery while receiving ether. Normal and ether-treated animal material was also examined and the effect of the ether found to be insignificant. These workers reported a loss of ganglion cells in 2 of their 11 cases and changes in ganglion cells in all 11. These changes included swelling and shrinkage of the cytoplasm, which "resemble changes frequently observed in association with chronic infections and metabolic disorders." Thus one cannot say, from the histopathological picture, whether these changes "are the cause of the psychosis, whether they are a consequence thereof or whether they are mere lateral effects of other factors influencing the central nervous system, without direct relation to the psychosis."

Kelly in 1924 [6] described the use of a special staining technique which enabled him to demonstrate irregularities in the outlines of the nucleus and nucleolus in 7 out of 10 cases studied, along with alterations in staining properties of the neural cells in these subjects. Of 32 "normals" investigated, only 2 showed similar changes; but it should be noted that all 7 positive cases in the experimental series suffered from tuberculosis, while only 2 of the 30 negative normal cases were thus afflicted. Kelly was content to ignore this interesting parallel, though with doubtful justification. There was evidently no effort made in this work to evaluate the effects of age or chronic disease on the findings.

One of the more elaborate reports concerning the disappearance of neuronal elements was that of Morgan and Gregory in 1935,[7] which dealt with a series of 32 cases of various psychoses, including 12 of schizophrenia. All 12 patients were found to have suffered a loss of 40% or more of the cells of the substantia grisea, and 11 of the 12 showed less than 25% normal cells in that structure by comparison with normal brains. Six control subjects were employed, one of whom died of pulmonary tuberculosis, two of diabetes, and three of trauma, including one case of cranial fracture. More than half the experimental patients were over 60 years of age, and some were over 80. In addition, the authors pointed out that "a preponderant number" had signs of arteriosclerotic changes in the cerebral vessels, but because four cases without such findings showed the neural lesions, they felt that the vascular pathology "is not sufficiently significant to account for the marked pathological changes noted in the series presented here." This conclusion is open to question.

In a subsequent paper Morgan (1940) [8] reported on 21 postmortem studies of the brains of patients with variously diagnosed psychoses obtained after death from a variety of chronic, acute, infectious, toxic, and traumatic conditions. The average age of the subjects in the series was 45, and the author found a 22% cell loss in the substantia grisea and a 39% loss in the nucleus tuberis lateralis. Cell counts were

made by microscopic fields and by comparison with similar fields in material from an unspecified set of "normal" sections. Morgan seemed to feel that the losses were diffuse and involved one type of cell rather than any specific areas. In addition, he noted that these changes are "characteristic of epilepsy and the psychoses and . . . diabetes mellitus."

An earlier report [9] described the findings in a series which included only one case of schizophrenia, in which similar cell losses were found in the substantia grisea and nucleus tuberis lateralis.

Myelin sheath changes were described in 1936 by Marcus [10] in six schizophrenics. He found demyelination of neuronal processes in the lenticular and basal ganglia especially, and less markedly in other sections. The loss of myelin produced empty, rounded "foyers" in the affected tissues. There were no signs of infectious or inflammatory changes, and Marcus suggests that the demyelination is a consequence of a "special toxic" action which he does not specify. The details of the cases used in this series are not presented, and no information is offered concerning their physical conditions or ages.

In a series of three cases reported in 1934 and 1943 Ferraro * described changes similar to those presented by Marcus, although in Ferraro's series the changes were considerably more diffuse. In addition, he found losses of and degenerative changes in the nerve cells "scattered everywhere." These changes consisted of swelling, disintegration, formation of "shadow" cells, and the presence of metachromic materials around the injured cells. Ferraro emphasized that the alterations were degenerative rather than inflammatory and that two of the three cases had family histories of schizophrenia. Control material, if used, was not mentioned.

One of the best-designed experiments in the recent literature is that of Bamford and Bean,[13] who rejected all cases in which the subject was more than 40, in which there was any sign of intercurrent disease, in which the death had not been acute, and in which there was any doubt concerning the psychiatric diagnosis of schizophrenia. These criteria eliminated all but three subjects from the series, but in all three they found "exhaustion changes," chromatolysis of the Nissl substances, and enlargement and pale staining in the Betz cells, which changes, however, they did not consider characteristic of schizophrenia. These workers also remarked on the "infantile state of the cardiovascular system" in these cases, as did Rupp and Wilson.[4]

Rowland and Mettler (1949),[14] in considering the frequent reports of neuron-cell "dropping out" which have appeared in the literature, pointed out that the cells in these investigations rarely were actually counted, that different methods of fixing and staining, different section thicknesses, different brain areas, different sources of material, and different criteria for countable cells have been employed, making it impossible to draw reliable comparisons among the reports of different workers. In their own series of 22 schizophrenic patients they attempted to relate the findings in material taken at lobotomy procedures to the severity and duration of the disease in those subjects. They found no significant difference in actual cell counts of comparable areas similarly treated and no relation to the severity or duration of the disease, age of the patient, electroencephalographic findings, or therapeutic use of insulin, electroshock, or pentylenetetrazol (Metrazol). Their work appears to be the

* References 11 and 12.

most authoritative reported and throws considerable doubt on the numerous, less carefully designed investigations which have reported cellular loss in schizophrenic brains.

In another well-designed investigation Dunlap,[22] in 1928, reviewed reports in the literature claiming to have demonstrated a "dropping out" of neural elements and attempted to verify these observations by making actual cell counts on uniformly prepared sections from the cortices of schizophrenic patients and by comparing these counts with those made on similarly treated normal brains. He and his co-workers were unaware of the source of the material that they were counting during the course of the investigation. These workers were unable to demonstrate any difference between control and experimental material and pointed out that a loss of nerve cells of the proportions described by some writers would produce a significant gross reduction in brain mass unless accompanied by a compensatory increase in some other component of nerve tissue. The glial cells have been implicated in such a proliferation, but Dunlap and others, working with no information regarding the source of the material examined, were unable to demonstrate important changes in the total mass, the glial elements, or the neural cells of brains from schizophrenics.

Comment on a stimulating but overenthusiastic publication by Southard in 1919[15] will serve to close this section. This investigator, on grounds which appeal to us even now as extremely speculative, suggested that there is a correlation between the location of "congenital" anomalies in the brains of schizophrenics and the clinical manifestations exhibited in a given case. He reported having found such defects in 80% of the schizophrenic brains he examined and in only 20% of those from manic-depressive patients; he insisted that where such lesions are not found, one is likely to find microscopic changes in nerve cells in the same areas of the brain. He postulated a relationship between subtle behavior changes and lesions in the superficial layers of the cortex, between delusion formation and lesions of the parietal and temporal lobes, and between catatonic states and the lower ("older") layers of the temporal and parietal lobes. This doubtful simplification of cortical topography and its functional activity was roundly denounced by Cheney[16] in his 1919 review and illustrates the danger of speculation well beyond the limits permitted by the state of our knowledge concerning the function of the cortex in schizophrenia.

2. *Changes in the Oligodendroglial, Astrocytic, and Microglial Elements.*—Publications dealing with reported histopathological findings in schizophrenia have implicated the glial components of the brain with almost as great a frequency as the neural elements. It is well known that the glial elements are sensitive indicators of a great variety of disease states, both those primarily of the central nervous system and those primarily of other systems. The lability of these elements in the face of many affections should encourage an attitude of caution in efforts to link such glial changes to the functional psychoses; that such caution was not uniformly exercised in the work presented here will soon be clear.

One of the earliest and most complete discussions of this problem was presented by Orton in 1914.[17] Included in his series was a group of 10 schizophrenics, ranging in age from 29 to 83 years and with a duration of mental disease ranging from 8 months to 46 years. Unfortunately, no mention was made of the terminal events in these patients, nor was their physical condition or the presence of acute or chronic diseases noted. In this series of 10 cases of schizophrenia, Orton described an increase in the ratio of satellite cells to neural cells in Layers 2 to 5 of the cortex,

which was exceeded only by the ratios found in manic-depressive patients. Comparison was made between different diagnostic groups; normal controls were evidently not employed. Orton remarked in closing that satellitosis of the kind described is found in all types of psychosis, and that the minor quantitative differences are not significant, and certainly not diagnostic, of schizophrenia. The duration of the disease did not affect the ratio, but the age of the patient did vary with the degree of satellitosis.

In a report in 1926 on necropsy material Penfield and Cone [18] reported finding swelling and other degenerative changes in the brains of psychotic patients. Suggesting that postmortem changes might be responsible for such alterations, Elvidge and Reed in 1938 [19] repeated Penfield and Cone's work, using biopsy material. Their series consisted of the following types: schizophrenia, 13; manic-depressive psychoses, 5, and "encephalitis, type unknown," 1. The age range was from 20 to 40 years, and the subjects were considered free of somatic disease when the samples were removed during lobotomy procedures. Second specimens were removed one to two years later in 7 of the 19 cases. Sixteen biopsy specimens from nonpsychotic patients undergoing brain surgery and biopsy material from 14 healthy laboratory animals were used as controls. The anesthetics used apparently were without effect in the material studied. Specimens were taken from the right and left parieto-occipital regions in all cases. In 16 of the 19 experimental cases a marked swelling of the oligodendroglial cells was found, with no correlation to the diagnostic category of the subjects. Second specimens, removed one to two years later, showed the same alterations in the seven cases examined a second time. Of the three negative cases, two were of uncertain clinical diagnosis, and one showed oligodendroglial alterations at a second biopsy. Eleven of the 16 control cases were negative; and of the 5 positive cases 2 had status epilepticus, 1 had a severe birth injury, 1 showed scarring from chronic sinusitis, and the fifth suffered from cerebral atrophy and hemiplegia. The findings in the laboratory animals were uniformly negative. The authors concluded that in patients who are mentally normal and in the absence of epileptic seizures, provided there is not an inflammatory or degenerative process in the area examined, no swelling of the oligodendroglial cells will be observed. Furthermore, they concurred with Penfield and Cone and stated [19]:

> By analogy with the other states in which swelling of the oligodendroglial cells is observed, it is justifiable to assume that in psychotic states also there may be a causal or metabolic factor [responsible for such changes].

In discussing the paper by Elvidge and Reed, Penfield stated:

> Oligodendroglial change means that an influence is at work that may be called toxic. In my [Penfield's] opinion, it indicates that the cause of the disturbance is outside the central nervous system only because it is usually seen in patients for whom this is obviously true.[18]

Along with a "dropping out of cortical neuronal elements," Rupp and Wilson [4] reported "chronic cell changes and reactive gliosis" in their series; Kirschbaum and Heilbrunn [5] found cytoplasmic or fibrous changes in the cortical microglial cells of all their series of 11 schizophrenics, oligodendroglial changes in 4, and an increase in the lipid content of glial cells in 6. They reported proliferation of protoplasmic astrocytes in all cases and enlargement of these elements in 7 of the 11 cases but pointed out that since pentylenetetrazol and insulin shock treatment can induce such

alterations, these data must be treated cautiously. Ferraro † reported "acute swelling" of oligodendroglial cells and glial proliferation, especially in the areas of demyelination he describes.

Winkelman and Book, in a communication appearing in 1949,[20] discussed their findings in postmortem material from 10 schizophrenics. These workers described moderate gliosis without signs of inflammation at the site of chromatolysis of neural cells, with a proportionality between the increase in astroglial elements and the damage to and loss of nerve cells.

Dunlap's carefully designed experimental work reported in 1924 [21] dealt with schizophrenics in whom the following criteria had been satisfied: The clinical diagnosis was verified by several competent psychiatrists; the patients were under 40; they died of acute processes without histories of chronic organic disease, and the postmortem specimens were taken immediately after death. Five controls were used who were without history of mental disease, had died of acute processes, and were submitted to autopsy immediately after death. As regards changes in the glial elements of the cortex, and other changes as well, Dunlap reported: "No changes have been found in [the schizophrenic groups] that were not duplicated exactly or in essentials by the control group." In a subsequent report published in 1928 Dunlap [22] repeated these observations and verified his earlier conclusions.

3. *Lipid Changes.*—Alterations in the lipid elements of the brains of schizophrenics, detectable by histopathological techniques, have been described by a number of writers. In most instances these alterations have been thought to be secondary to changes in other elements, notably the myelin sheaths of both white and gray matter, but some writers have described lipid accumulations under circumstances that suggest an etiology independent of lesions in the neural or glial components.

Cotton in 1915 [23] published one of the earliest, and perhaps still the most complete, description of lipid alterations in the psychoses. Among his postmortem specimens 20 were from schizophrenics, 10 from manic-depressive patients, and a smaller number from patients representing a variety of other psychotic states. Pointing out that alcohol and other agents were known to cause the deposition of lipid material in the neural, glial, and vascular elements of the brain long exposed to them, Cotton rejected cases with a history of alcoholism. Examining specimens from a series of normal subjects ranging in age from 16 to 70, all of whom had died in acute processes, Cotton noted that the Scharlach R stain showed a progressive increase in the lipid content of the ganglion cells with increasing age, and that there was no observable lipid deposition in the glial elements, ganglion cells, or perivascular tissue of brain material from infants. Thus, only a marked deposition of lipid materials, well beyond the expectation for the age of the subject, could be considered significant; and, even when such a deposition is found, the many toxic and other conditions able to induce such accumulations must be eliminated before conclusions are drawn concerning the significance of lipid accumulations in schizophrenia. Cotton, with these reservations ostensibly in mind, wrote, "We conclude that in dementia praecox a profound degree of fatty degeneration in all cells of the cerebral cortex is found," with the most marked deposition of lipid material in the glial, neuronal, and vascular elements of the second and, especially, the third cortical

† References 11 and 12.

layers. Similar alterations were noted in the brains of manic-depressive patients and, most markedly, in those suffering from senile dementia, but changes reportedly occurred earlier in schizophrenia and more frequently affected the axis cylinders and their myelin sheaths. Unfortunately, many of the subjects in Cotton's series died of tuberculosis, often after chronic courses. The effects of this condition, and possibly of other disease states in the patients whose physical health was not described, cannot be evaluated in weighing the significance of the lipid changes Cotton reported. Cotton concluded with the suggestion that the excessive fatty deposits seen in these brains are due to a flaw in the metabolic process which normally removes lipid materials before such accumulations can occur, rather than to an increase in the production of lipid by the degeneration of neural elements.

The "grape-like clusters" of dissolved lipid described by Buscaino [1] and subsequently shown to be artifacts of fixation in alcohol by Ferraro were further investigated by Freeman,[2] who found that such "lesions" were never seen in material treated with formalin regardless of the clinical state of the subject in life, while typical "clusters" could be found in the brains of normal subjects dying in accidents when the material was subjected to alcoholic fixation. Material from schizophrenic brains, sectioned and fixed in alcohol and mounted in paraffin, showed these clusters in the globus pallidus in 67% of the 24 examined, while only 43% of the 21 brains from patients with dementia paralytica and 43% of the 30 brains from patients with cerebral arteriosclerosis showed these clusters. The changes were not correlated with age, sex, race, cause of death, delay in removal of the material after death, or fixing time in alcohol. Freeman believes that while there is evidence of the effect that intracellular lipid deposits are more marked in the brains of schizophrenics and appear at an earlier age in these patients, the particular configuration described by Buscaino is an artifact and lipid deposition is not characteristic or diagnostic of schizophrenia.

Ferraro,[11] in a description of the findings in the brain of a 14-year-old boy, diagnosed as a case of schizophrenia two years before his death, of pneumonia, reported finding perivascular accumulations of lipid-laden gitter cells, which the author apparently considered secondary to the marked degenerative alterations seen in the ganglion cells of the cortex. Similar degenerative deposits, perivascular or independent of the vascular system, have been described in relation to demyelination (Marcus [10]) and as diffusely scattered throughout the brain by Winkelman and Book,[20] Spielmeyer,[3] and Dunlap.[22] Vogt and Vogt [24] described lesions in the medial nucleus of the thalamus in catatonic schizophrenics which they interpret as early fatty involution and consider as primary alterations, preceding the clinical manifestations of the disease. Bamford and Bean,[13] however, in their series of three carefully selected cases, found no evidence of lipid accumulations in the ganglion cells of the cortex or in other locations.

4. *Changes in the Vascular and Perivascular Structures.*—Alterations in the vascular and perivascular tissues, while reported with less frequency than those changes already described, have been noted with sufficient frequency to merit special consideration. As was the case with lipid changes, lesions of these structures have generally been reported in association with and secondary to changes in the ganglion cells and glial elements, but in a few instances it was the opinion of the investigators that vascular and perivascular alterations were themselves the primary cerebral pathology.

Rupp and Wilson [4] in their series of brains from psychotic patients, including 20 schizophrenics and 11 with manic-depressive psychoses, reported unspecified cerebral vascular lesions in 9, calcification of cerebral vessels in 7, and congenital malformations of the circle of Willis in 18. Unfortunately, the incidence of these interesting findings in the schizophrenic group per se is not given, and the authors have apparently not determined the frequency of such alterations, congenital or acquired, in normal brains.

Bruetsch in 1938 [25] described a series of 280 consecutive postmortem examinations on patients in a hospital for mental diseases in which endocarditis was found in 18 (6.4%). Of these 18 cases, 10 without complications such as syphilis or cerebral arteriosclerosis were presented, in 9 of which were found organic brain lesions sufficient, in the author's judgment, to have caused the clinical picture seen in each case. Of the nine in this group, a diagnosis of manic-depressive psychosis was made during life in two, and of schizophrenia in four. The lesions discovered in these brains were cerebral infarctions, with septic infarctions in those cases of subacute bacterial endocarditis. Bruetsch also pointed out that such lesions were found in 8% of cases diagnosed as "functional psychoses" and in only 1% of those diagnosed as "organic psychoses." While there is no suggestion that such massive lesions are involved in the classical case of schizophrenia, such findings emphasize the variety of causes which can produce the clinical picture of schizophrenia and the importance of careful attention to diagnostic criteria in assembling material for study in investigations such as these. In this regard it is interesting to recall that Rupp and Wilson [4] found 7 cases of congenital cardiovascular anomalies in a series of 37 cases of schizophrenia and 36 cases of organic cardiovascular diseases in the same series. Freeman,[2] reporting on the findings in 100 consecutive cases with autopsy, of which 24 were of schizophrenia, remarked:

> The frequency and the early age at which calcification occurs in schizophrenia were remarkable. It seems doubtful in schizophrenia as well as in the other pathological conditions whether the terminal condition had anything to do with the condition of the vessels.

This worker found such calcification most frequently in the globus pallidus of the brains examined.

Ferraro,[12] reporting on a single case of schizophrenia, noted a thickening of the adventitia of vessels in those areas in which demyelination was pronounced; and Bamford and Bean [13] reported a generalized congestion of the brain in their series, without, however, comparing these findings with those seen in brains from normals dying with the same kinds of acute processes. Ferraro,[11] as previously noted, reported perivascular accumulations of lipid-laden gitter cells in a single case of schizophrenia in a young boy.

5. *The Work of Papez, and Papez and Bateman.*—The publications of this pair of investigators dealing with the histopathology of schizophrenia are treated separately in this review both because the nature of their findings does not permit a reasonable division into the structural categories employed and because the chronological development of their work forms such an important and interesting aspect of their contribution.

Descriptions of intraneuronal inclusion bodies are rare in the earlier literature on the histopathology of the brain in schizophrenia. Such structures are, of course, commonly found in the viral encephalitides, and there are infrequent descriptions of

inclusion bodies in other diseases of the central nervous system (Marburg, 1943).[26] In 1944, however, Papez [27] reported finding intracytoplasmic inclusion bodies in a variety of nervous system affections, including spastic paralysis, chronic chorea, and "disturbances recorded as terminating in psychosis." Using special staining methods, he described these structures as 1 to 4 $\mu$ in length and 1 or 2 $\mu$ in diameter and suggestive of "living protein bodies or particles capable of multiplying into colonies in the cytoplasm of the nerve cell, of living in symbiosis with the nerve cell for a long period and, when discharged from a disintegrated cell, of migrating in groups, and sometimes singly, in the nerve tissue." The neuron cells infested with these bodies were described as vacuolated, granulated, and showing evidence of metabolic disturbances. When liberated from the neuron cells, the bodies were reported to migrate toward vessels, where they entered the cytoplasm of perivascular cells, formed perivascular cuffs, and underwent degeneration to yellow or black pigments. Papez denied that the bodies were artifacts and reported that they were occasionally found in the brains of supposedly normal subjects. He also considered "the absence of inflammatory reaction" about these bodies "noteworthy."

In 1948 Papez published a report [28] in which he described neuron cell inclusions in biopsy material from cases of scrub typhus, anterior poliomyelitis, dementia praecox (11 cases), chronic (unspecified) psychoses, and multiple sclerosis, among others. In this series he reported finding progressive degenerative changes in the cells infested with these bodies, such changes including vesiculation of the nuclei, destruction of Nissl granules, and, ultimately, complete loss of cytoplasm in heavily infested cells. He reported that from 50 to 90% of the cells in the thalamus and cortex were affected in some degree by this process and described a concurrent swelling of oligodendroglial cells. Migration of the inclusion bodies to perivascular cuffs was again described. In another report published in 1948 Papez [29] reported his findings in a series of cortical biopsies which included specimens from 29 patients with schizophrenia. Control material from laboratory animals and normal adults and children was entirely negative, but material from schizophrenic subjects again showed progressive degeneration of neuron cells associated with the inclusion bodies and culminating in a complete loss of cytoplasm in the more heavily attacked cells. Naked nuclei reportedly formed 50 to 85% of the nerve cell population in certain areas of the cortex and were most frequent in Layer 5. Papez and Bateman, in a paper published in 1949,[30] described their findings in the brains of patients with tsutsugamushi fever. The intracellular, extracellular, and perivascular inclusion bodies and the degenerative change in the neuron cells in these descriptions are similar to those previously reported in a variety of affections of the central nervous system, including schizophrenia. In the same year these workers [31] reported the results of an investigation of lobotomy material from 42 patients with the diagnoses of schizophrenia and again described intraneuronal, extracellular, and perivascular bodies which were associated with severe cellular degeneration in a large but unspecified proportion of the cases examined. This degenerative process was described in three stages: (*a*) the intact stage, with nuclear deformity and rod- or comma-shaped inclusion bodies in the pale-staining cytoplasm; (*b*) with large, round, "inflated" nuclei surrounded by rims of cytoplasm containing the inclusion bodies, and (*c*) naked nuclei, which had lost all cytoplasm and, with it, the inclusion bodies. Stage *a* was most characteristic of schizophrenia and accounted for more than 50% of the cell population in most cases. Stage *c* was interpreted as a sign of nuclear

effort toward repair and replacement of the lost cytoplasm. The authors estimated that approximately five years elapsed between stages, that the second stage represented clinical episodes of remission and recurrence, and that the third was related to permanent dementia. They suggested that these changes represent an acute metabolic disorder, as though an abnormal stimulus to protein synthesis, perhaps from the inclusion bodies, caused first an acceleration in protein production, followed by exhaustion of the capacity to synthesize this material. In 1950 Papez and Bateman [32] published a report in which they described similar changes in the cells of the thalamic nuclei in necropsy material from 31 cases of several types of psychosis. Similar changes found in normal control brains were much less marked, and the writers state:

> There was never any question of far advanced cell pathology in cells of the various thalamic nuclei in all 31 cases studied. Our specimens showed that disease of the cortical cells was associated with all manner of nuclear disease in the thalamus. Psychoses may be interpreted as functional expressions of thalamic and cortical disease in varying pathological patterns or combinations.

Papez in 1950 [33] presented the results of observations on sections taken during gyrectomy procedures on five schizophrenic patients and again described inclusion bodies and degenerative changes in the nerve cells of Brodmann Areas 9 and 10, particularly in Layers 3, 4, and 5 of the cortex. In 1951 Papez and Bateman [34] presented their findings from 70 biopsies on schizophrenic patients. For the first time these workers stated that the inclusion bodies described are "live, actively moving" organisms and suggested that "the different forms of this strange pleomorphic organism represent a life cycle of an encapsulated larval parasite capable of invading or multiplying in the nerve cells." They also suggested that the cellular effects noted are due to a disruption of the normal protein metabolism of the cells and "intensive ribonucleic acid production and growth of cell proteins," representing an "accelerated early stage of production of growth-promoting nucleoproteins." Degenerative changes in the cells are accompanied by moderate gliosis and neuronophagia.

The most recent stage in these investigations was reported in a paper by Papez [35] which appeared in 1952. Phase-contrast examination of biopsy material from 30 psychotic patients and autopsy material from 102 cases of psychosis of unspecified types, courses, and durations, carried out on saline suspensions of cortical material obtained and prepared under aseptic conditions, reportedly showed great numbers of living, reproducing colonial organisms in filamentous, rod-like, globular, lashing, cystic, sac-like, and other forms, in neurons, extracellularly and within erythrocytes. Papez describes a complex reproductive cycle, intracellular and erythrocytic phases, and large colonies resembling the Nostoc blue-green algae and states that the granular forms previously described in stained preparations were "old, dead zooid organisms surrounded by fats."

These remarkable findings, thus far unverified by other investigators, defy critical evaluation at this time. Merely the unusual nature of the claims must not be allowed to interfere with open-minded consideration of the findings or of subsequent reports by these or other workers, but it is clear that at this stage little can be said concerning the significance or importance of these reports. Many questions remain which can be answered only through carefully designed experimental work with adequate

attention to controlled observations on rigorously selected material, eliminating as far as possible the effects of contamination, concurrent disease states, artifact, and the insidious influence of preconception.

### III. COMMENT

Despite the efforts of some of the ablest investigators in psychiatry and neuropathology during the past half-century, the question whether there are characteristic brain lesions associated etiologically with the clinical manifestations of schizophrenia has not been answered. The literature dealing with this problem, while voluminous, is marked by inconclusiveness and contradiction, in large part due to inadequate attention to the design of the experimental work and insufficient caution in analyzing and interpreting the results thereof. A large number of reports have described the "dropping out" of neuron cells, particularly in the deeper layers of the cortex in brains from schizophrenics. Considered only from the point of view of the number of such reports in the literature, this phenomenon would appear to be strongly established as a characteristic finding in a significant proportion of such brains, but closer scrutiny indicates that the majority of such reports lack one or more of the criteria of reliable investigation and interpretation discussed in the introduction to this review. Those publications which deny having observed this cellular loss, while fewer in number, are for the most part based on procedures which command more respect for the design of the investigation and, thus, for the results obtained. While a loss of cortical neuronal elements stands out as the most frequent finding reported, and while such a lesion might by speculation be implicated in the variegated clinical manifestations of schizophrenia, there is as yet no definitive work on which such an implication can be based.

Those workers who have suggested that the glial elements of the brain are characteristically altered in schizophrenia face, if such a comparison can be made, even greater technical and interpretative difficulties than those who have described changes in the nerve elements, for a great variety of diseases and metabolic disorders not primarily involving the central nervous system induce changes in these labile components. The significance of reported lesions in the glial elements are meaningless in terms of their relationship to schizophrenia unless it can be shown that all of the numberless "other conditions" which can and do transform these elements have been controlled in the work described. In none of the reports discussed in this review has this difficult condition been met; indeed, it may be beyond the current capacity of medical investigation to fulfill these demands. But it is clear that until and unless such controls can be applied to investigative findings, such reports can be interesting, but not conclusive. The same rigid standards must be met in work reporting on lipid alterations and vascular changes associated with schizophrenia. In addition, the former findings are meaningless without careful evaluation of the possible role of metabolic disorders and a variety of therapeutic and toxic agents which can induce lipid changes in the brain chronologically and etiologically independent of the clinical manifestations of schizophrenia. Vascular lesions must obviously be interpreted with the complex question of superimposed, primary vascular or cardiorenal diseases always in mind, but this precaution has been taken by few of the workers reporting on vascular and perivascular lesions in the brains of schizophrenics.

In view of the lack of definitive evidence in any of these categories or in others, the question of a characteristic histopathology of schizophrenia remains unanswered. Moreover, there is no commanding reason to assume that there are or need be such characteristic lesions, for there is much doubt that the clinical diagnosis of schizophrenia in reality encompasses a single disease entity, even if one accepts for the present the hypothesis that schizophrenia in any form is an organic disorder or group of disorders. Ferraro [12] notes, "The recent trend to consider schizophrenia not as a disease entity but as a syndrome resulting from more than one etiologic factor is in harmony with the accumulating experience," and Hassin [27] remarks, "It is questionable whether even the changes described . . . are not secondary, due to the long duration of the disease with its unavoidable complications."

The very confusion and diversity which mark the literature in this field during the past half-century suggest, however, a point of departure which has only recently been recognized. It is unwise to lose sight of the possibility that a search for histopathological alterations in schizophrenia may, in fact, amount to an investigation on the wrong level and that the definitive lesions in many or most cases clinically diagnosed as schizophrenia may be metabolic rather than gross, or even microscopic. When one is faced with a relatively characteristic clinical picture, associated with either the absence of any characteristic gross or histopathological changes or an unpredictable variety of such changes, the likelihood that metabolic dysfunction is associated causally or as the result of one or more of these changes must be entertained and fully investigated. For those unwilling to accept the hypothesis that schizophrenia is necessarily a functional disorder and unable to acknowledge as conclusive any of the descriptions of histopathological changes discussed, the approach to this problem must take a new direction. The very inconclusiveness of the results obtained in the long search for microscopic lesions points toward investigations into the metabolic activity of the brain in schizophrenia as the most reasonable and promising approach to the problem of the dynamics and etiology of this disease.

## IV. SUMMARY

1. The technological and interpretative precautions which must be exercised in investigations concerning histopathological changes in the brain in schizophrenia are discussed.

2. The literature dealing with such changes in the neurons, glial elements, lipid components, and vascular and perivascular tissues is reviewed. A special section describes and comments upon the work of Papez and Papez and Bateman.

3. The findings described are discussed in relation to the design of the investigative procedures used, the precautions necessary for interpreting such findings, and the implications which can be drawn from the contradictory and inconclusive results of 50 years of investigation on the histopathological level.

4. It is suggested that for those who reject the "functional" classification of schizophrenia, the very lack of definitive results from the histopathological approach dictates a new attack on the problem of the etiology of schizophrenia from the level of metabolic dysfunctions in the brain.

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# SARCOIDOSIS WITH INVOLVEMENT OF THE NERVOUS SYSTEM

## Report of Nine Cases

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SINCE Boeck [1] in 1899 first described the skin lesions that have since come to bear his name, a large number of accounts of the disease have appeared in the literature.

The disease is known by a variety of names, of which sarcoidosis, benign lymphogranulomatosis, and Besnier-Boeck-Schaumann disease are the commonest. The condition described by Heerfordt [2] under the title of "febris uveo-parotidea subchronica," later known as Heerfordt's syndrome, has now come to be recognized as a special manifestation of the same disease.

The early history of the disease has been fully reviewed by Hunter,[3] Pautrier,[4] Gravesen,[5] Leitner,[6] and others. Although Boeck was the first to describe the histological characteristics of the skin lesions, Hutchinson (cited by Hunter [3]) had already published a clinical description of such a case in 1875 and of two others in 1898. It was Schaumann,[7] however, in 1914, who first showed that Boeck's sarcoid of the skin and the various forms of combined symptoms reported were part of a generalized disorder.

The etiological agent is unknown. Many features of the disease suggest that it is due to a chronic infection. The relation of sarcoidosis to tuberculosis has been intensively studied. The etiological hypotheses have recently been reviewed by Rostenberg.[8]

A survey of the pertinent literature discloses that sarcoidosis of the nervous system is very rare. Gravesen,[5] in his series of 150 cases of sarcoidosis, found only 7 with signs of nervous system involvement; of these, 5 had peripheral facial paralysis, 1 had Horner's syndrome, and 1 had diabetes insipidus. Ricker and Clark,[9] in a clinicopathological study of 300 consecutive cases of sarcoidosis, found evidence of nervous system involvement only in 2%. The organs most frequently affected were lymph nodes, 83%; lungs, 76%; skin, 21%; bone, 17%; eyes, 9%; liver, 9%, and spleen, 8%. The liver and spleen are probably affected far oftener than is evident from clinical reports. In autopsy series * invasion of these organs has been reported in from 60 to 70% of the cases.

The frequency of neurological complications in Ricker and Clark's series accords well with the observations of Löfgren.† This author found signs of nervous system involvement only in 2 out of 300 cases of sarcoidosis, that is, less than 1%. His series, however, consisted predominantly of patients in the "primary" stage of the

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* References 9 and 10.

† Löfgren, S.: Personal communication to the author.

disease, with erythema nodosum and/or bilateral hilar lymphadenopathy, and of a minority in the "chronic" stage. It seems probable that sarcoidosis of the nervous system might be found more frequently if the cerebrospinal fluid (CSF) were examined routinely. This supposition is supported by the studies of Carstensen and Norvitt,[11] who, in a series of 15 cases of sarcoidosis, found 6 with pleocytosis and increased protein in the CSF; of these, only 2 had signs of nervous system involvement.

Colover,[12] in 1948, collected the reports of 112 cases from the literature and added 3 of his own with manifestations of nervous system involvement. Similar, though less exhaustive, surveys have been made by Pennell[13] and Essellier and co-workers.[14]

Reports from the literature and experiences in the present series make it clear that there are no signs and symptoms which can be said to be pathognomonic of sarcoidosis and that variable clinical pictures, referable to the organs and tissues involved, must be expected.

Some authors distinguish a meningitic, an encephalitic, and a polyneuritic type of sarcoidosis. This is a very crude and superficial method of classification, and many clinicopathological pictures cannot be grouped under these designations.

The commonest sign of nervous system involvement is the peripheral type of facial paresis, which is often recurrent. The central nervous system may develop a meningoencephalitis or meningomyelitis or may be affected by tumor-like masses in the dura mater, manifested clinically by generalized disturbances of cerebral function. Localized infiltration by sarcoid tissue may be manifested clinically by focal cerebral dysfunction.

## REPORT OF CASES

CASE 1.—S—g, a man aged 25, was admitted to the Neurological Clinic of Serafimerlasarettet in January, 1952.

In 1950 routine roentgenographic examination of the lungs revealed a few patches of linear density of undetermined nature scattered irregularly throughout both lungs. Tuberculosis could be ruled out.

He was asymptomatic until December, 1951, when he noticed loss of vision in the right half of both visual fields, associated with tiredness, lack of initiative, and mental sluggishness. About two weeks later his mental status altered for a brief period to one of mild exaltation.

*State on Examination.*—His mental status was normal. Physical examination disclosed a few enlarged lymph nodes and splenomegaly. He was afebrile. The Mantoux reaction to 1 mg. of tuberculin was negative. The sedimentation rate ranged from 5 to 10 mm. in one hour. The serum protein was normal. A chest roentgenogram showed no essential change from the film taken in 1950. A biopsy specimen from an affected lymph node showed changes suggesting commencing tuberculosis, with no evidence of necrosis or caseation, although the possible presence of sarcoid could not be excluded (Dr. Falconer). Guinea pig inoculation and Lowenstein culture of lymph node tissue were negative. A roentgenogram of the hands showed no bony changes. Neurological examination revealed no abnormality except right homonymous hemianopsia. A pneumoencephalogram and carotid arteriogram demonstrated two poorly vascularized expanding processes in the anterior part of the left frontal region and in the region of the left Sylvian tissue (Figs. 1 and 2). The electroencephalogram showed focal abnormality suggesting a process in the left frontal lobe. (Fig. 3*A*). The CSF contained 89 lymphocytes and 100 polymorphonuclear leucocytes per 3.2 cu. mm. Total protein was 76 mg. per 100 cc.

*Treatment.*—A total of 5,000,000 units of penicillin was given during his first 10 days in the hospital on account of the spinal fluid abnormalities; the possible presence of a cerebral abscess could not be excluded on initial examination. No other medication was given.

*Clinical Course.*—The hemianopsia gradually receded (Fig. 4). Two months after admission a pneumoencephalogram showed marked regression of the pathological processes (Fig. 1*C* and *D*); the electroencephalogram was normal (Fig. 3*B*), and the CSF showed normalization.

When seen in January, 1953, he was asymptomatic. Neurological examination revealed nothing abnormal.

Case 2.—P—n, a man aged 50, was admitted to the Neurological Clinic of Serafimerlasarettet in June, 1950.

His general health had been good until the summer of 1949, when profound psychic changes took place, i. e., tiredness, apathy, and lack of judgment, and he became unclean and disorderly. At this time he was admitted to the local hospital, where examination revealed generalized

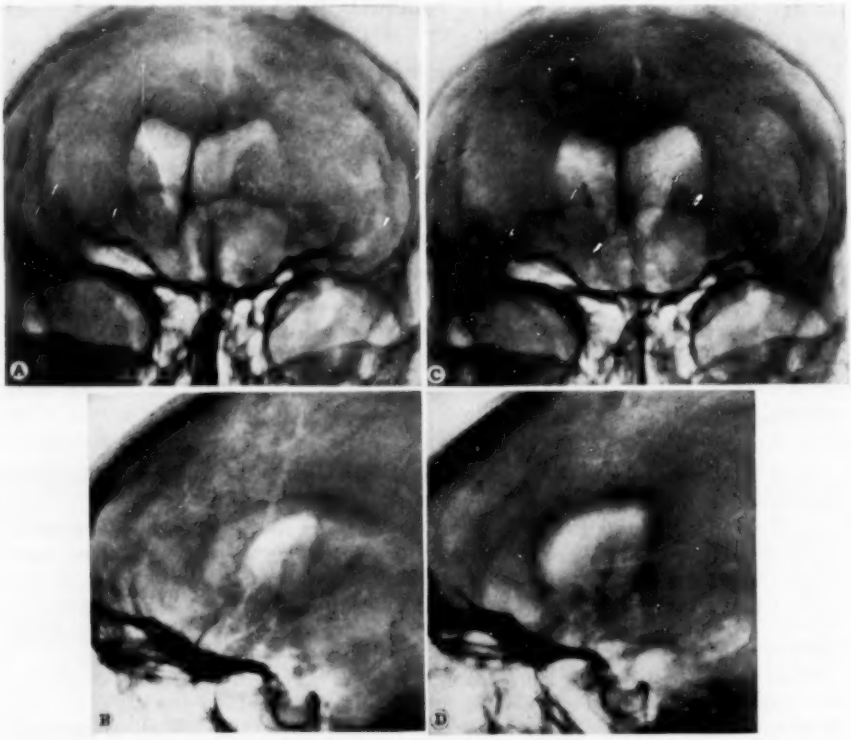

Fig. 1 (Case 1).—Pneumoencephalograms. *A* and *B* (Feb. 7, 1952): considerable dislocation of the ventricular system to the right. The left frontal horn is dislocated backward. Conclusion: expanding process in the anterior part of the left frontal lobe.

*C* and *D* (April 7, 1952): now only slight dislocation of the ventricular system, with no dislocation of the left frontal horn.

lymphadenitis and hepatomegaly. A roentgenogram of the chest demonstrated bilateral enlargement of the hilar lymph nodes. A lymph node biopsy specimen was diagnosed as questionable sarcoid. In May, 1950, he was transferred to a mental institution and found to have hemiplegia. He became steadily worse and increasingly lethargic. In June he was transferred to the Neurological Clinic.

*State on Examination.*—The patient was found to be semicomatose and unresponsive. Neurological examination revealed left facial paresis of the central type and left hemiplegia. The ocular fundi were normal. A carotid arteriogram demonstrated a large expanding process in the right temporal lobe. Operation was carried out immediately.

*Operation* (Dr. E. Bohm).—The upper portion of the inferior horn of the right lateral ventricle was filled with a grayish-red mass, measuring about 2 by 3 cm., arising in the choroidal plexus and projecting into the posterior part of the horn, which was grossly dilated. The mass was extirpated and a gush of cerebrospinal fluid obtained. On gross inspection the surgical specimen resembled a choroidal papilloma. The structure contained a small number of cavities occupied by irregular wandering tissue macrophages with scanty covering cells. The specimen probably had its origin in the choroid plexus.

*Microscopic Examination* (Dr. I. Lundholm).—There was no evidence of tumor tissue, but changes of an inflammatory character were revealed. The connective tissue was the seat of gross changes, with scattered foci of calcification. There was marked cellular infiltration, consisting predominantly of rounded tubercles made up of epithelioid cells and occasional giant cells, some of the Langhans type and some of the foreign body variety, with little tendency to confluence. The cut surfaces often showed a thick wall of collagenous fibrils in the periphery of the nuclei. No tendency to necrosis was observed. No acid-fast rods were seen in the sections. The histological picture closely resembled that generally seen in benign lymphogranulomatosis, though the

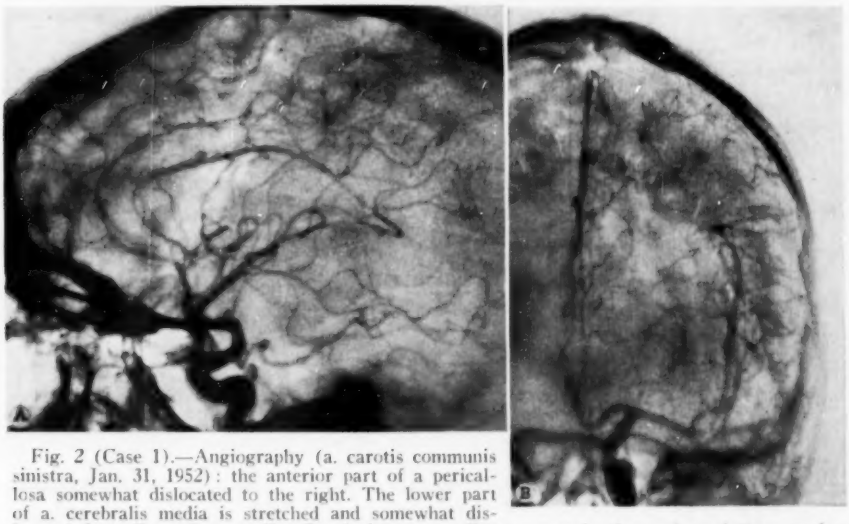

Fig. 2 (Case 1).—Angiography (a. carotis communis sinistra, Jan. 31, 1952): the anterior part of a pericallosa somewhat dislocated to the right. The lower part of a. cerebralis media is stretched and somewhat dislocated frontally and upwardly. Conclusion: expanding process in the region of the anterior part of the Sylvian fissure.

possibility of a tuberculous etiology could not be excluded. The histological diagnosis was inflammatory tissue changes compatible with those in Schaumann's disease.

The postoperative convalescence was uneventful.

The follow-up investigation in July, 1952, at the Östersund Hospital (Dr. I. Lundholm had made the patient's records available) disclosed that he had on the whole remained well since his discharge from the hospital. In 1951 he had had a few grand mal seizures and occasional attacks of mild gastric disturbances. Repeated CSF studies showed pleocytosis and considerably increased protein. The count varied from 16 to 90 cells per 3.2 cu. mm., almost exclusively lymphocytes, and the total protein, from 140 to 300 mg. per 100 cc. In November, 1950, serum proteins measured 6.3 gm. per 100 cc., with 4.3 gm. of albumin and 2 gm. of globulin per 100 cc. The skin of the left ear lobe showed a bluish discoloration, which had been present since 1950. He still showed signs of mental dullness but had commenced to work. Enlarged lymph nodes, hilar lymphadenopathy, and hepatomegaly were still present.

Case 3.—M. T.—g., a woman aged 35, was admitted to the Neurological Clinic of Serafimerlasarettet in February, 1948.

Her general health had been good until 1939, when she had transient attacks of peripheral facial paresis, first on the left side and later on the right, accompanied by swelling of the parotid glands and ageusia. In 1940 she noticed uveitis, along with a recurrence of transient attacks of facial paresis and parotitis. Chest roentgenograms demonstrated bilateral enlargement of the hilar nodes and fine mottled parenchymal densities diffusely scattered throughout both lungs. The Mantoux reaction to 3 mg. of tuberculin was negative. The sedimentation rate was 8 mm. She had a low-grade fever. From 1941 to 1946 she was symptom-free. In February, 1947, she began to have frequent headaches along with a return of transient attacks of facial paresis.

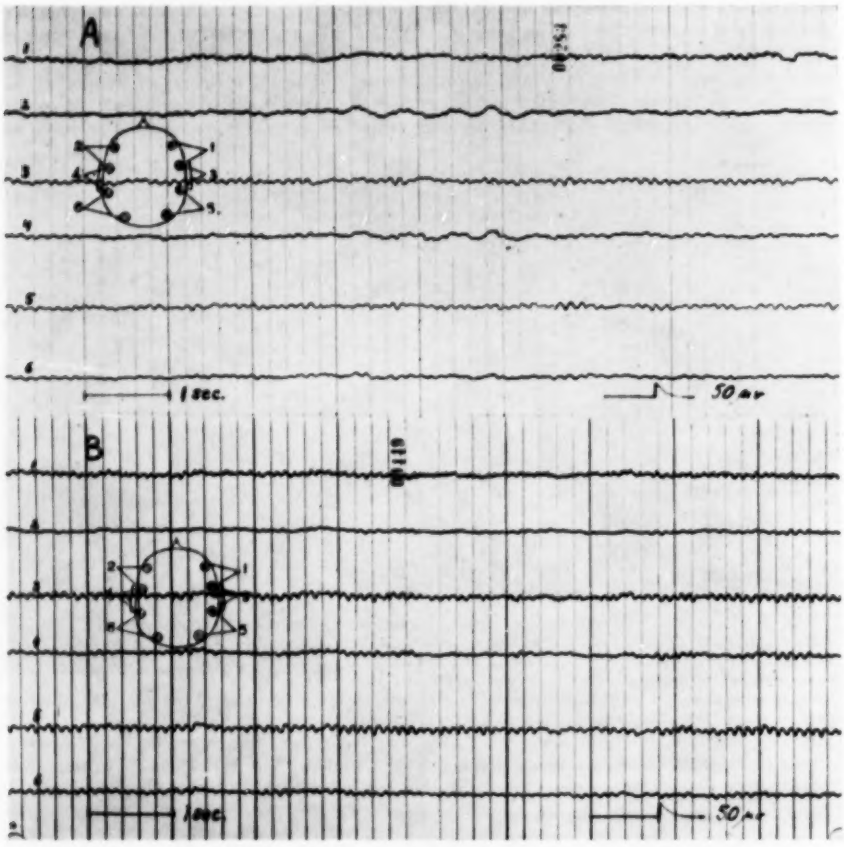


Fig. 3 (Case 1).—*A*, EEG (Feb. 5, 1952): in the anterior part of the left hemisphere a large number of 2-3 cps waves with an amplitude of up to 50 μv. Conclusion: focus signifying a process in the anterior part of the left frontal lobe. *B*, EEG (April 1, 1952): no definite evidence of abnormality.

A few months later she noticed amenorrhea, polydipsia, and polyuria (approximately 5 liters a day). At the same time there was a return of uveitis, accompanied by headaches, bilateral deafness, rotary vertigo, and peripheral facial paresis.

*State on Examination.*—Her mental status was normal. Physical examination disclosed inguinal lymphadenitis. Chest roentgenograms showed slight regression of the hilar masses as compared with the picture in 1940. The parenchymal densities had acquired a streakier appearance. She had a low-grade fever. The sedimentation rate ranged from 16 to 19 mm. in one hour.

The Mantoux reaction to 1 mg. of tuberculin was negative. Serum proteins measured 7.4 gm. per 100 cc., with 5.8 gm. of albumin and 1.6 gm. of globulin per 100 cc. Urinary output varied from 2 to 5.5 liters per day. The urine contained no sugar or albumin. The fasting blood sugar was normal. Neurological examination revealed right peripheral facial paresis with slight contracture bilaterally. There was marked bilateral deafness of neurogenic type. Her gait with the eyes closed was unsteady. There was no paralysis. There was an extensor plantar response on the left. Examination of the eyes revealed chronic uveitis. The CSF contained five lymphocytes and four polymorphonuclear leucocytes per 3.2 cu. mm.

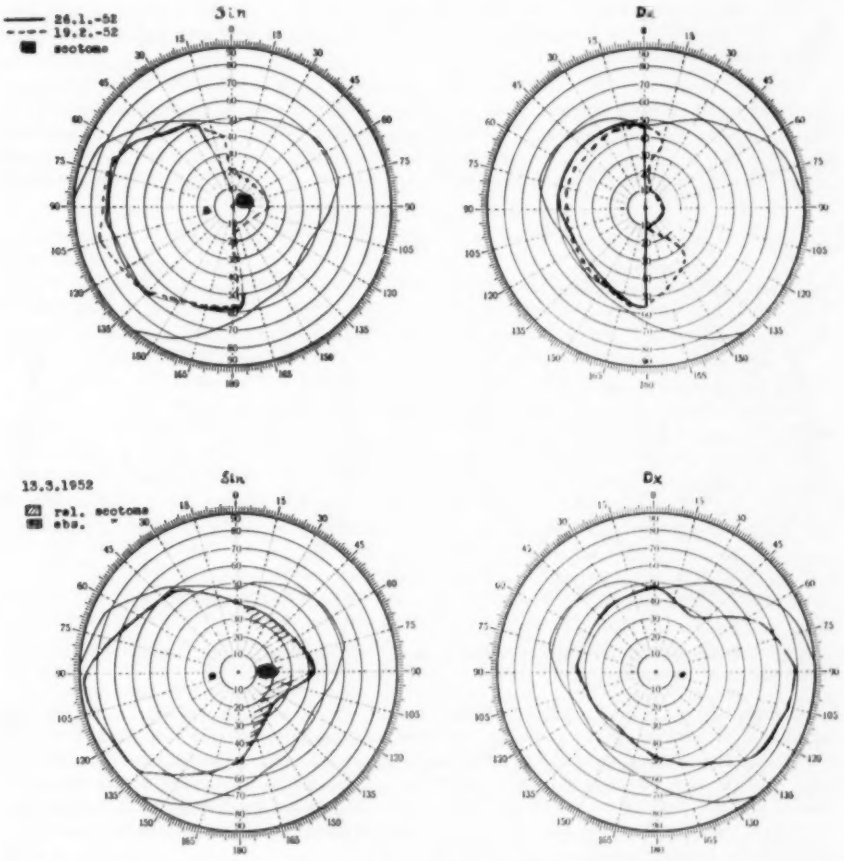


Fig. 4 (Case 1).—Visual fields: right homonymous hemianopsia; considerable improvement within six weeks.

The follow-up investigation in 1952 disclosed that about a month after her discharge from the hospital the polydipsia and polyuria began to subside and gradually disappeared completely. Her diabetes was then of six months' standing. She had had a few transient attacks of facial paresis but had, on the whole, felt well. Neurological examination revealed no abnormality.

Case 4.—N. A. K., a woman aged 45, was admitted to the Neurological Clinic of Serafimerlasarettet in October, 1947.

Her general health had on the whole been good until December, 1946, when she noticed marked impairment of vision in the left eye and pain above the eye. Her vision improved but in

March, 1947, again deteriorated. In August, 1947, she was able to count fingers at 2 meters' distance with the left eye. Perimetry showed concentric constriction of the left field of vision and defect of the lower nasal quadrant. The left optic disc was edematous on initial examination but subsequently was pale.

Since May, 1947, she had had repeated attacks of mucopurulent rhinitis, with the formation of nodules in the nasal mucosa. In August, 1947, a biopsy specimen from the nasal mucosa (Dr. Reuterwall) disclosed numerous epithelioid tubercules with central necrosis and occasional Langhans giant cells. The histological diagnosis was specific inflammatory changes compatible with either tuberculosis or Schaumann's disease. In September, a chest roentgenogram (Dr. E. Fornell) demonstrated bilateral hilar lymphadenopathy and small mottled densities in both lung fields. The condition was diagnosed as sarcoidosis. The patient was examined at the Neurological Clinic of Serafimerlasarettet.

*State on Admission.*—Her general condition was good. There was no definite enlargement of the lymph nodes. Roentgenograms of the spleen and small bones of the extremities showed normal conditions. She was afebrile. The Mantoux reaction to 0.01 mg. of tuberculin was negative; to 1 mg. of tuberculin it was questionably positive, the area measuring 8 by 10 mm. in size. The sedimentation rate changed from 22 to 25 mm. in one hour. Serum proteins measured

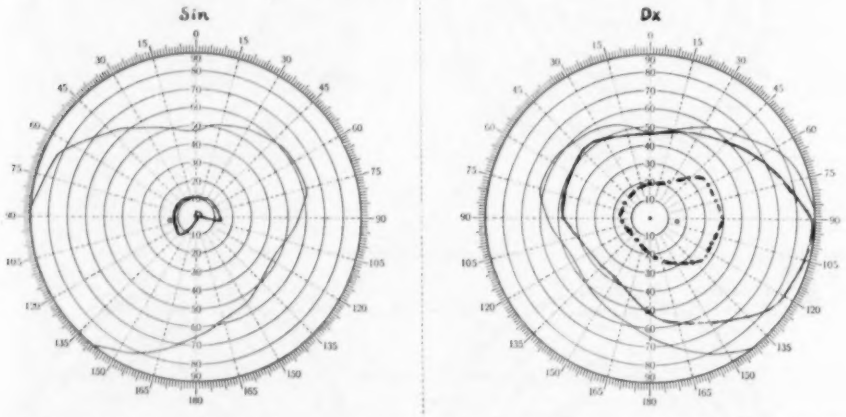


Fig. 5 (Case 4).—Visual fields: right, normal; left, concentric constriction with defect of the lower nasal quadrant.

5.7 gm. per 100 cc., with 4.3 gm. of albumin and 1.4 gm. of globulin per 100 cc. Guinea pig inoculation of ventricular washings was negative. A tonsil biopsy specimen showed normal conditions. Neurological examination: Vision was 1.0 in the right eye and 0.1 or 0.2 in the left eye. The left optic disc was pale, with elevation of 1 D. Perimetry showed marked constriction of the left field of vision of the tubular type and lower quadrantal nasal hemianopsia (Fig. 5). Vision in the right eye was normal. A roentgenogram of the skull and an encephalogram showed normal conditions. The CSF was normal.

In 1952 the patient wrote that she was managing unaided and had not required hospitalization during the past five years. No new neurological disturbances had appeared. She often felt tired. Walking uphill and climbing stairs made her breathless. She often had a thick mucous discharge from the nose and throat.

Case 5.—G. E. M., a woman aged 59, was admitted to the Neurological Clinic of Serafimerlasarettet in August, 1948.

In 1933 she contracted tuberculosis in the apex of both lungs; the disease had remained quiescent for the past several years. In June, 1948, she wakened one morning with a brief attack of severe dizziness and felt that the bed was spinning around in the room. During the following month she experienced diffuse dizziness, which persisted to a diminishing degree, and sometimes a tendency to stagger toward the side.

*State on Examination.*—Apart from slight intellectual deficiency, her general condition was good. She had a low-grade fever. The sedimentation rate was 73 mm. in one hour. Splenohepatomegaly was present. Serum proteins measured 7.8 gm. per 100 cc., with 4.3 gm. of albumin and 3.8 gm. of globulin per 100 cc. Sternal marrow examination revealed no abnormality. A roentgenogram of the chest demonstrated mottled and linear parenchymal densities in the upper portion of both lungs, extending down to the level of the hilus, characteristic of tuberculosis. The condition was unchanged as compared with the examination one year previously. A punch biopsy specimen from the spleen showed epithelioid tubercles with well-formed Langhans giant cells throughout the entire organ (Fig. 6). There was no evidence of necrosis but a tendency to fibrosis. The condition was diagnosed as sarcoidosis (Dr. Falconer). Neurological examination: The pupils were irregular and unequal, fixed to light, and sluggish in convergence-accommodation. The right ankle jerk was absent. The neurological status was otherwise normal. The CSF was normal. The Wassermann reactions of the blood and spinal fluid were negative.

In 1952 the patient wrote that she was at the time entirely symptom-free. Reactivity in the left pulmonary apex had necessitated sanatorium care for six months during the period 1950-1951. The report from the sanatorium stated that small, fresh parenchymal deposits had appeared in the left pulmonary apex. Acid-fast rods had been recovered in ventricular washings. A check-up examination six months after discharge was negative.

Case 6.—A. J. F., a man aged 34, was admitted to the Neurological Clinic of Serafimerlasarettet in June, 1949.

His general health had been good until 1943-1944, when he noticed obstruction of the nasal passages, which had troubled him ever since. At the same time he noticed swelling of the cervical lymph nodes and, later, of the inguinal nodes also. In 1944 a chest roentgenogram demonstrated bilateral enlargement of the hilar nodes compatible with a diagnosis of sarcoidosis.

In 1944 he underwent extensive surgical treatment of the nasal mucosa on account of the formation of crusts, which were then interpreted as of tuberculous nature. Repeated cultures were negative for tubercle bacilli but, on the other hand, yielded Aspergillus. Roentgenograms of the hands disclosed no bone lesions. Repeated Mantoux tests with 1 mg. of tuberculin were negative. Guinea pig inoculation of ventricular washings was negative. In 1945 histological examination of an excised lymph node led to the diagnosis of sarcoidosis (Dr. Zettergren).

Since 1947 he had had frequent attacks of paresthesiae in the form of tingling, numbness, and stiffness, which generally began in the perioral region and spread to the right arm and hand, and usually also to the right leg. The paresthesiae sometimes occurred on the left side also. The attacks were usually accompanied by difficulty in speech, and sometimes with generalized headache. He often had headaches between the attacks and occasionally weakness of the right arm. The attacks lasted from 15 to 60 minutes and sometimes terminated with nausea. On one occasion in 1948 he experienced tingling over the whole body and clumsiness of the right hand. He felt he had no control over his tongue and was able to utter only simple short words, such as "yes" and "no." A couple of days later he showed evidence of agitation and mild visual hallucinations, seeing men and animals around him at night. The condition cleared up 48 hours later. The CSF contained 13 cells per cubic millimeter (11 lymphocytes and 2 polymorphonuclear leucocytes); Pandy positive; Nonne negative. He was admitted to another hospital at this time, with a diagnosis of chronic encephalitis.

*State on Admission to the Neurological Clinic.*—His general condition was good. He was afebrile. His right cheek had a skin eruption typical of sarcoid. The sedimentation rate was 45 mm. in one hour. He was mentally slow and ixophrenic. He had difficulty in following the conversation, although the customary functional tests were performed fairly well. Neurological examination revealed incoordination in the finger-nose and knee-heel tests. Perimetry was normal. A roentgenogram of the skull revealed no abnormality. An encephalogram showed the left lateral ventricle to be somewhat wider than the right; there were no other abnormalities. The electroencephalogram was abnormal, with general dysrhythmia but no evidence of a focus.

In 1952 the patient wrote that he then only rarely had mild attacks of numbness but often suffered from headaches. He had returned to work.

Case 7.—J. E. V., a woman aged 63, was admitted to the Neurological Clinic of Serafimerlasarettet in 1946.

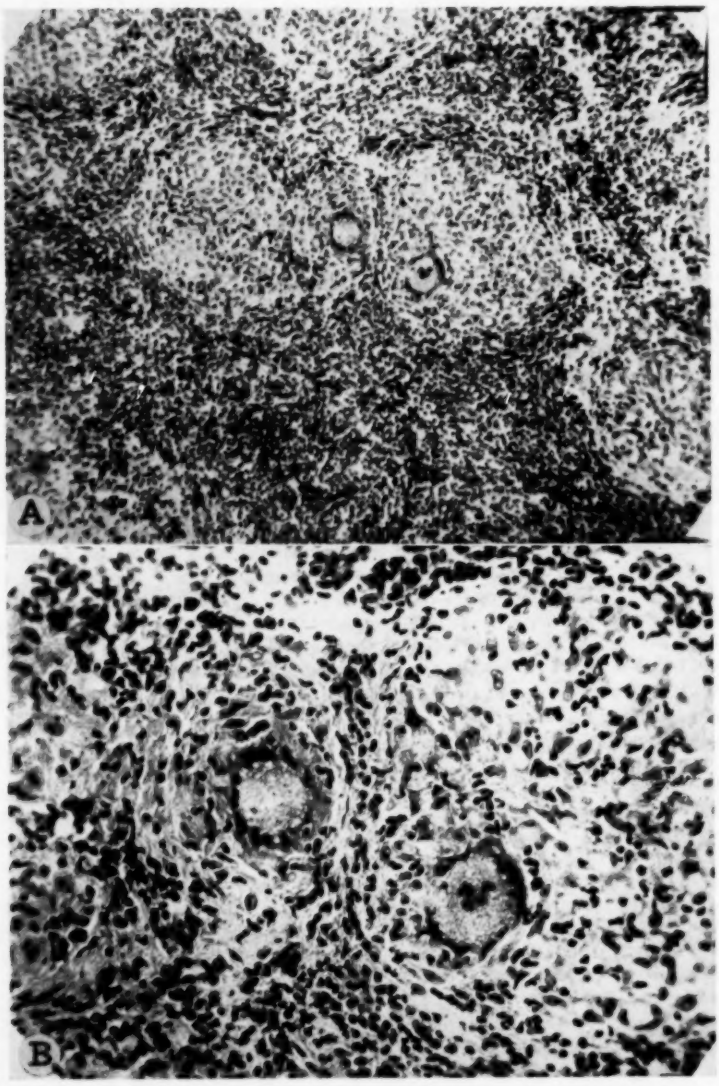


Fig. 6 (Case 5).—Photomicrograph of a punch biopsy specimen from the spleen. *A*, epithelioid tubercles with well-formed Langhans giant cells; no evidence of necrosis. *B*, sarcoidosis. Hematoxylin-eosin stain; × 115 and × 290, respectively.

Except for hemicrania as a girl, her general health had always been good. In 1944, at the age of 61, she noticed bilateral iridocyclitis, followed shortly by dizziness and gait disorders of uncharacteristic type, which disappeared a few months later. About a year after the onset of her illness she again experienced dizziness and gait disturbances, accompanied by profound right-sided deafness. Improvement of hearing some time later was associated with very troublesome tinnitus localized "inside the head." She became easily fatigued and periodically had sleep disturbances. This was manifested by a period of abnormal somnolence, followed by a period of insomnia. Later she noted right-sided peripheral facial paresis, which rapidly regressed. She complained of marked impairment of memory, irritability, and nervousness. Since the onset of her illness she had had a low-grade fever. She was examined at the local hospital, where the CSF showed a slight pleocytosis (10 lymphocytes per cubic millimeter). Her condition was interpreted as encephalitis.

*State on Examination.*—The mental status showed intellectual deterioration and impaired memory for recent events. Concentration was poor; the 100-to-3 test was impossible. Her general condition was good. She looked pale but was not anemic. She had a low-grade fever, which persisted throughout her stay in the hospital. The sedimentation rate ranged from 22 to 29 mm. in one hour. There were isolated enlarged lymph nodes. The Mantoux reaction to 0.1 mg. of tuberculin was negative. A roentgenogram of the chest showed parenchymal densities, varying from a lentil to a pea in size, scattered throughout both lungs. Diagnosis, sarcoidosis. Her physical status was essentially the same as noted on examination about one year earlier. Neurological examination revealed no definite paresis or sensibility disturbances apart from slight loss of vibratory perception in the legs. She had a staggering, unsteady gait of uncharacteristic type. Ophthalmoscopic examination revealed iridocyclitis and chronic amblyopia. Opacities in the vitreous humor precluded satisfactory examination of the fundi, but they were probably normal. Vision was 0.2 in both eyes. There was bilateral impairment of hearing, more pronounced on the right, resembling the neurogenic type, with sluggish caloric reactions. The CSF was normal.

In 1952 the patient wrote that since her discharge from the hospital she had been able to manage unaided and had not required hospital care. She was still troubled with tinnitus and occasionally with mild dizziness.

CASE 8.—S—r, a man aged 30, was admitted to the Neurological Clinic of Serafimerlasarettet in February, 1952.

His general health had been good until January, 1952, when he noticed left-sided peripheral facial paresis. In February numbness developed in the left arm and coldness in the fingers. Vision was blurred in the left eye, and he had difficulty in swallowing. He felt tired and nervous.

*State on Admission.*—Physical examination revealed slight general malaise and fatigue. Small lymph nodes were palpable on the neck, and one, the size of a bean, in the left axilla. The sedimentation rate ranged from 7 to 11 mm. in one hour. He had a low-grade fever throughout his five-week stay in the hospital (temperature never above 100.4 F.). The Mantoux reaction to 1 mg. of tuberculin was negative. Total serum proteins measured 7.7 gm. per 100 cc., with 5.1 gm. of albumin and 2.6 gm. of globulin per 100 cc. Pulmonary roentgenograms showed bilateral hilar lymphadenopathy. Roentgenograms of the hands revealed no bony changes. Sternal marrow examination showed plasma cell reaction and marrow eosinophiles. A tonsil biopsy specimen showed normal conditions. Examination of the mental status revealed poor concentration and slight emotional imbalance, his behavior alternating from mild exaltation to unwarranted uncommunicativeness. Mental calculation was poor. There were no psychotic reactions. Neurological examination revealed iritis in the left eye. Vision was 1.0 in each eye. He had left-sided peripheral facial paresis. The pharynx showed a suggestive *signe de rideau* on the right. There was slight left-sided hemianesthesia, including the distribution of the left trigeminal nerve, and a suggestive left hemiparesis. The CSF contained 8 lymphocytes and 2 polymorphonuclear leucocytes per 3.2 cu. mm. Total proteins measured 18 mg. per 100 cc. A roentgenogram of the skull, a pneumoencephalogram, and a cerebral angiogram (right carotid and verterbral arteries) showed normal conditions. The electroencephalogram revealed nonspecific generalized abnormality with a slow dominant rhythm.

*Clinical Course.*—The subjective neurological symptoms gradually subsided during the next few months. In April, 1952, there was minimal iritis in the left eye, but the right eye showed

evidence of iritis with exudates in the aqueous chamber, which later cleared up. Repeated chest roentgenograms showed an unchanged picture. The sedimentation rate returned to normal within six months. The Mantoux reaction was persistently negative.

CASE 9.—R. T. A., a woman aged 38, was admitted to the Neurological Clinic of Serafimerlasarettet in May, 1943.

At the age of 25 she had had mild symptoms of hyperthyroidism with raised metabolic rate. Her general health had otherwise been good.

At the age of 34 (1938) she noticed swelling of the cervical lymph nodes for a period of two months. At the same time she was very tired and suffered from headaches and vomiting, which have recurred periodically ever since. A cervical lymph node biopsy specimen was diagnosed as sarcoid (Dr. L. Santesson). Roentgenograms of the lungs and small bones of the hands showed normal conditions. The Mantoux reaction to 0.01 mg. of tuberculin was positive. In March, 1943, she had a brief attack of central facial paresis with weakness of the left leg, on account of which she was admitted to Serafimerlasarettet a couple of months later.

*State on Examination.*—Her mental status was normal. Physical examination disclosed no enlargement of the lymph nodes. Roentgenograms of the lungs and small bones of the extremities showed normal conditions. The blood pressure was 175/120 mm. Hg. The oculi fundi showed evidence of early hypertensive retinopathy. The urine was normal. She was afebrile. The sedimentation rate was normal. The encephalogram was technically poor, and no air entered the ventricles. Air was present in slightly widened sulci on the convexities of the brain. The CSF contained 9 lymphocytes per 3.2 cu. mm.; the protein content was not raised.

The follow-up investigation revealed that the patient had died two and a half years after her discharge from the hospital, that is, at the age of 41, at another hospital in Stockholm. The cause of death was stated to be chronic nephritis, bronchopneumonia, and pulmonary infarction. Autopsy was not performed.

*Comment.*—In this patient the appearance of symptoms of sarcoidosis was accompanied by severe headaches and vomiting. The CSF was not studied at this stage of her illness. It is not improbable, however, on the basis of the clinical picture, that mild involvement of the brain and/or meninges had occurred. The case was complicated by hypertonia. Therefore the cause of the transient hemiplegia is not certain. Autopsy was not performed.

## COMMENT

1. *Mental Symptoms.*—That invasion of the central nervous system by sarcoid lesions may be declared by variable mental symptoms is not surprising. In the present series five patients exhibited either mild or severe symptoms of mental disorder. In one patient (Case 2) the symptoms were so severe that commitment to a mental institution was necessary. Profound mental changes—apathy, lack of judgment, and gradual neglect of his person—had developed during a period of one year, and he gradually fell into a semicomatose condition. Laboratory investigations revealed increased intracranial pressure, caused by an obstructing lesion in the inferior horn of the right lateral ventricle. Surgical intervention was followed by marked regression of the symptoms. One patient (Case 6) showed evidence of agitation and visual hallucinations for a period of a few days. Examination approximately one year later disclosed mental dullness, dependence, and difficulty in following the conversation. Case 7 complained of profound impairment of memory and irritability. Examination revealed intellectual deterioration, impaired memory for recent events, and poor concentration. Easy fatigability, lack of initiative, irritability, and mild exaltation were noted in two patients (Cases 1 and 8). Mental symptoms reported in the literature include a psychasthenic syndrome, character changes, lethargy, and psychotic features with persecution ideas,[18] and confusional states.

2. *Cerebral Symptoms Resembling Those in Cerebral Tumor, in Hypophyseal Lesions, and in Hypothalamic Lesions; Other Cerebral Symptoms.*—Cerebral

Tumor: Cases 1 and 2 illustrate how sarcoidosis can produce symptoms resembling those in cerebral tumor. In Case 1 it was the appearance of homonymous hemianopsia that first led the patient to seek medical assistance. A pneumoencephalogram and carotid arteriogram revealed expanding processes in the left frontal lobe and in the region of the left sylvian fissure. This case beautifully illustrates the rapidity with which these significant expanding sarcoid processes may regress. To judge from the clinical manifestations in this alert and intelligent man, a law student, it is probable that the growth of the process had also been relatively rapid. It should be noted that signs of increased intracranial pressure were not present.

Case 2 had a comparatively small tumor which, owing to its situation, caused an obstruction in the inferior horn of the right lateral ventricle and produced profound mental symptoms, as well as signs of increased intracranial pressure. Granulomatous masses in the choroid plexus do not appear to have been previously observed.

Sarcoid lesions in the meninges have been found in a number of cases that came to autopsy. Naumann's [16] case serves as an illustration. His patient was a 3-month-old infant (a remarkably young age for sarcoidosis) with hepatosplenomegaly and cutaneous eruptions of the sarcoid type. The child had convulsions, neck rigidity, and pleocytosis in the CSF and died after six weeks' illness. At autopsy typical sarcoid lesions were found in the subdural layer of the falx, in the tentorium cerebelli, and under the sutures of the skull. Both the pachymeninges and the leptomeninges were infiltrated.

Apparently any part of the brain may be invaded by sarcoid tissue. Lenartowicz and Rothfeld [17] described a case that came to autopsy in which sarcoid lesions were found in the infundibulum, optic chiasm, left temporal lobe, lenticular nucleus, right caudate nucleus, and hypothalamus. Localized sarcoid lesions show, however, a predilection for the base of the brain.

Hypophyseal Lesions: Involvement of the pituitary gland appears to be especially common. In Case 3 diabetes insipidus developed seven years after the first sign of nervous system involvement (facial paresis). Amenorrhea occurred at the same time. The diabetes was mild and gradually subsided, disappearing completely at the end of six months. Endocrine function studies performed later (Dr. Luft) showed a return of normal pituitary function.

Tillgren [18] described a case that came to autopsy in which the pars media of the pituitary gland was invaded by sarcoid tissue.

Pennell [13] found diabetes insipidus to be a prominent symptom in 18 (35%) of 51 cases of sarcoidosis with involvement of the central nervous system reported in the literature. In 2 of the 18 cases an adiposogenital syndrome was also exhibited.

Hypothalamic Lesions: Case 7 in this series experienced a period of profound sleep disturbances about a year after the first appearance of neurological symptoms. This was manifested by a period of excessive sleepiness, which lasted approximately six months, followed by a period of insomnia. Marked hypersomnia has been recorded, among others, by Guillain.[19]

Other Cerebral Symptoms: In Case 6 unilateral paresthesiae, sometimes associated with weakness of the homolateral arm, aphasia, headache, and nausea, developed four years after the onset of symptoms of sarcoidosis. Although the symptoms

appeared chiefly on the right side, they sometimes appeared also on the left. The clinical picture resembled in certain details that of the migraine syndrome. The patient was 32 years of age at the time and had not previously had hemicrania. At the same time there was evidence of mental symptoms and a slight pleocytosis in the CSF. Disseminated infiltration of the brain was probably present. Case 8 also had paresthesiae, which did not, however, come in attacks but persisted for a period of about one month and then disappeared completely.

Other symptoms of cerebral disorder described in the literature include epilepsy,‡ unilateral sensory deficits,[22] extrapyramidal syndrome, cerebellar symptoms, and variable disseminated cerebral symptoms.

*Cranial Nerve Lesions.*—The facial nerve is the most commonly affected. Four patients in the present series had peripheral facial paresis; in one of them it was recurrent. A perusal of the literature shows that there is still a tendency to attribute the facial paresis to direct pressure on the nerve by an enlarged parotid gland. This, however, is incorrect. Facial paresis may occur in the absence of parotitis and is sometimes associated with ageusia. Anesthesia in the facial distribution of the trigeminal nerve was noted in one patient (Case 8). Transient neurogenic deafness was recorded in two patients (Cases 3 and 7), and involvement of the pharynx and soft palate, in one (Case 8). According to the literature, sarcoid lesions have been found in practically every cranial nerve at one time or another.

*Ocular Lesions, Including the Optic Nerve.*—Iritis was noted in three patients in the present series (Cases 3, 7, and 8). Iridocyclitis is a comparatively common manifestation of sarcoidosis. In Gravesen's [5] series of 734 cases 14% had iritis. In approximately one-half of them it was accompanied by swelling of the parotid glands and/or other salivary glands. It would seem, however, that the incidence of iritis is substantially higher in patients with than in patients without signs of nervous system involvement. Thus Colover [12] recorded iritis in 56% of his series of 118 cases. This means, then, that uveitis may be expected to occur four times as frequently in cases of sarcoidosis with as in those without manifestations of neurological involvement. The lesions generally heal completely, though this may take months or even years, but serious sequelae, such as cataracts and glaucoma, have been reported. Levitt [24] described phthisis bulbi as the sequela in 10 out of 100 cases culled from the literature. Other ocular lesions described are choroiditis and choroidoretinitis, as well as retinal perivasculitis [23] and periphlebitis.§

Case 4 in this series had recurrent papillitis. Similar cases have been recorded.‖ Slight swelling of the optic disc, usually up to 1 D., appears to be comparatively common. A tumor in the optic nerve has been described in rare cases, in which it has caused considerable elevation of the optic disc, in one case up to 20 D.[28]

In Case 5 an Argyll Robertson pupil was the only sign of ocular involvement; there was also unilateral loss of the ankle jerk. Loss of pupillary reaction to light combined with multiple neurological symptoms, signifying widespread infiltration of the brain, has been reported in one patient.[29] A case of Adie's syndrome, with tonic pupils and absence of muscle reflexes, has been attributed to sarcoidosis.[30] However, these pupillary anomalies appear to be very rare.

‡ References 20 and 21.

§ References 24 and 25.

‖ References 26 and 27.

*Cerebrospinal Fluid.*—A marked pleocytosis and elevated protein were noted only in two patients in the present series. In Case 1 the lumbar spinal fluid contained 189 cells per 3.2 cu. mm., with an insignificant predominance of polymorphonuclear elements. Total proteins measured 76 mg. per 100 cc. In Case 2 the cell count varied from 16 to 90 per 3.2 cu. mm., and the protein content, from 140 to 300 mg. per 100 cc. In four patients there was only a slight pleocytosis. In two patients the CSF was normal. In one patient (Case 9) the CSF was not examined at the time of her illness; a later investigation revealed normal conditions.

Pennell,[13] among others, has made a survey of the cerebrospinal fluid changes in sarcoidosis reported in the literature. Spinal fluid changes appear to be present in approximately 50% of cases of sarcoidosis with neurological complications. The commonest abnormalities are a moderate pleocytosis and a moderate, less often marked, increase in protein. The cells present are usually lymphocytes, though small numbers of polymorphonuclear leucocytes may occasionally be present. A protein content of 720 mg. per 100 cc. was noted in a single instance. A significant lowering of the sugar content of the CSF was recorded in a small number of cases.

## TREATMENT

No specific therapy is yet available. Arsenic was used previously, but the results were equivocal. The application of carbon arc radiation and Finsen light has been reported to have some, but questionable, effect on the cutaneous lesions. Nitrogen mustard, urethan and antibiotics, including streptomycin, have proved ineffective. More recently, calciferol (vitamin $D_2$) has been used, apparently with favorable influence on both the cutaneous and the mucous membrane lesions, while it exerted no demonstrable effect on the lesions of the lungs, the lymph nodes, or the skeleton.[31] Toxic evidence of hypercalcemia limits the usefulness of the agent. Corticotropin and cortisone have also been used for the past two years.¶ The reports are still too few and conflicting to permit any conclusion as to the efficacy of this treatment. Cases have been described, however, in which both the neurological and other symptoms have shown marked regression during the treatment (Carstensen and others). If these early results are sustained, it means not only that an improved therapeutic agent for sarcoidosis is available but also that some new light may be shed on the pathogenesis of the disease.

None of the patients in the present series was administered treatment of the above-mentioned types.

## PROGNOSIS

In the majority of the nine patients in the present series it was the neurological symptoms that first led them to seek medical assistance. In two cases, however, symptoms of sarcoidosis had been present in other organs for one and four years, respectively. The average length of follow-up observation from the onset of neurological symptoms was five years. At the follow-up investigation in 1952, all the patients were alive except one, who had died of intermediate disease. In the majority of the patients the neurological symptoms either had subsided or showed marked regression.

¶ References 11 and 32 through 41.

Vosbein [42] summarized the causes of death in 140 cases of sarcoidosis reported in the literature up to 1951. In 48% of the cases death was ascribed to sarcoidosis; in one-fourth of these, to lesions in the nervous system.

The prognosis as regards survival is generally good, even though, as has long been known, it is not entirely favorable. In cases in which the nervous system is involved the prognosis is somewhat poorer. Functional recovery, on the other hand, is poor, especially in regard to the eyes, heart, kidneys, and lungs. The pulmonary changes may lead to fibrosis of the lungs and chronic cor pulmonale.

## DIAGNOSIS

There is probably no other disease with such extensive dissemination which presents so few clinical manifestations. The subjective symptoms are usually vague, such as tiredness, malaise, cough, shortness of breath, loss of weight, anorexia, skin eruptions, enlarged lymph nodes, and ocular disturbances.

Sarcoidosis should be suspected in any patient in whom two or more of the following conditions are coincident.

1. Skin lesions. These generally take the form of disseminated nodules and plaque-like eruptions, most frequently on the face and extensor aspects of the limbs.

2. Mucous membrane lesions. These occur chiefly in the nasal mucosa as pale-yellowish nodules.

3. Enlarged lymph nodes. The nodes are variable in size, firm, tense, rubbery in consistency, and freely movable.

4. Pulmonary lesions. The diagnosis cannot be made on the basis of the roentgenographic findings alone. Perhaps the most characteristic picture is that of bilateral hilar lymphadenopathy and/or fairly symmetrical mottled infiltration, involving mainly the middle third of the lung fields. The pulmonary parenchymal changes may resemble not only various forms of tuberculosis but also a variety of conditions, including Hodgkin's disease, lymphosarcoma, carcinomatosis, silicosis, fungous infections, histoplasmosis, coccidioidomycosis, and eosinophilic infiltrates (Löffler).

5. Skeletal changes, roentgenographically appearing as characteristic circumscribed cystoid areas of rarefaction in the small bones of the extremities. Similar changes have been observed only in leprosy.

6. Swelling of the salivary glands, most frequently the parotid.

7. Ocular lesions: conjunctivitis; uveitis; less often choroiditis and retinitis. The uveitis may be chronic, with infiltrates, or transient, with insignificant symptoms, which are disclosed first on ophthalmoscopic examination.

8. Enlargement of the liver and spleen.

9. Neurological symptoms; cerebrospinal fluid changes.

10. Hyperproteinemia. The albumin-globulin ratio is often reversed.

11. Negative tuberculin reaction. This occurs in 60 to 70% of the cases.

*Clinical Course.*—Sarcoidosis tends to run a prolonged, sluggish course, ranging in duration from several months to many years, with alternate periods of progression and spontaneous regression. An intermittent, mild fever and a moderately raised sedimentation rate are generally present.

The diagnosis of sarcoidosis is usually made from the nature of the cutaneous eruptions and the lymphadenopathy, with or without the support of biopsy specimens from the skin, mucous membranes, lymph glands, or tonsils. Diagnosis has been made by punch biopsy from the spleen and/or liver on a number of occasions. The typical Kveim reaction is considered to be specific for cases of sarcoidosis. As a diagnostic test, however, it is markedly limited, since the reaction is slow to evolve, often requiring weeks to reach maximum size and persisting for many months.[43]

For diagnostic purposes Daniels [44] recommends bloc resection of the fat pad between the sternocleidomastoid and the anterior scalenus muscles. This fat pad contains small lymph nodes which communicate with the mediastinal lymphatic system. Norviit and his co-workers [45] succeeded with this method in confirming the diagnosis in 15 (71%) out of 21 patients with clinical and roentgenological suspicion of sarcoidosis but without palpable lymph nodes.

### DIFFERENTIAL DIAGNOSIS

Sarcoidosis may sometimes be confused with other infectious or systemic diseases which produce multiple symptoms. The clinical distinction may be difficult in the presence of neurological symptoms. Not infrequently the literature contains descriptions of clinical syndromes broadly included under a heading of the type "ophthalmoencephalitis" which lack a sound basis for the evaluation. These headings sometimes mask cases of sarcoidosis and other morbid conditions which should be recognized as clear-cut clinical entities.

Diseases with which sarcoidosis might be confused and which, like sarcoidosis, sometimes produce symptoms of nervous system involvement include tuberculosis, syphilis, polyarteritis nodosa, disseminated lupus erythematosus, infectious mononucleosis, histoplasmosis, toxoplasmosis, brucellosis (undulant fever), Behcet's syndrome, and Hodgkin's disease. The neurological manifestations in some of these diseases can scarcely be considered well known, since they are seldom or not at all mentioned in the textbooks. Consequently, a brief description of them is given here and the differential diagnosis discussed.

*Polyarteritis Nodosa.*—The considerable variability of the manifestations of this condition frequently poses a difficult problem in differential diagnosis. As in sarcoidosis, the onset of the disease is often insidious and the course is measured in years. The general health, however, is usually more affected than in sarcoidosis, and the prognosis is poor.

Hepatomegaly and splenomegaly are comparatively common. Involvement of the lungs is rarer than in sarcoidosis, and the pulmonary roentgenographic picture often resembles that in Löffler's eosinophilia. The skin manifestations generally appear as subcutaneous nodules, which represent the primary arterial lesion. Other skin manifestations frequently occur, however, and result in an exceedingly polymorphic picture. Fugitive erythemata, urticaria, purpura, and vesicular and bullous eruptions have been recorded. Involvement of the lymph nodes appears to be relatively rare. Ocular lesions in the form of conjunctivitis, choroiditis, retinal perivasculitis, arteriosclerotic retinitis, and, in rare cases, iridocyclitis have been noted. The nervous system is estimated to be involved in 20 to 25% of all cases. Prominent

features are pleocytosis in the CSF, meningitis, cerebral symptoms with generalized convulsions, and polyneuritis, generally associated with polymyositis, accounting for the frequent occurrence of severe pain. Hemiplegia, cerebellar signs, paraplegia, papilledema, optic atrophy, pupillary disturbances, and other signs of cranial nerve involvement, as well as of disseminated nervous system lesions, have been described.# The diagnosis is made by biopsy of subcutaneous nodules or affected muscle.

*Disseminated Lupus Erythematosus.*—A couple of years ago a case was admitted to the Neurological Clinic which presented difficulty in differential diagnosis. The patient, a woman aged 36, had a two-year history of tiredness, intermittent fever, oligomenorrhea, and, more recently, progressive weakness of the legs. Physical examination revealed a generalized grayish-brown pigmentation of the skin, acrocyanosis, cervical lymphadenitis, hepatomegaly, splenomegaly, serous pleuritis, and mild renal insufficiency. Neurological examination revealed bilateral papilledema, with elevation of 4 D. and flaccid paraplegia. The CSF showed a slight increase in protein; the cell count was normal. All investigations, including pneumoencephalography, cerebral angiography, and myelography, showed normal conditions. In differential diagnosis, sarcoidosis and polyarteritis nodosa were considered. Autopsy revealed disseminated lupus erythematosus.

The variability of the clinical course not infrequently offers difficulty in differential diagnosis. The salient clinical manifestations are a prolonged irregular fever, polyarthritis, characteristic skin lesions in the butterfly area of the face, and signs of pulmonary, cardiac, and renal involvement. Splenomegaly and hepatomegaly are common. Lymphadenopathy may be present. Neurological complications appear to be relatively rare but, when present, exhibit a picture of focal or disseminated encephalomalacia, involving primarily the gray matter of the cerebral cortex, the encephalomalacia being secondary to the specific endarteritis.[48] Papilledema and paraplegia may also be present, as exemplified by the case described above. Polyneuritis has been described.[49]

*Toxoplasmosis.*—Toxoplasmosis should be suspected in all newborn infants exhibiting signs of encephalitis, rash, jaundice, and hepatosplenomegaly, with or without hydrocephalus, microcephaly, or chorioretinitis, and in infants and children suffering from convulsions, hydrocephalus, microcephaly, or psychomotor retardation in conjunction with chorioretinopathy, with or without cerebral calcification. Thus, toxoplasmosis occurs at an age when sarcoidosis is exceedingly rare. Toxoplasmosis in adults presents a variable clinical picture, generally with pulmonary changes and in rare cases with generalized lymphadenopathy.[50]

However, the presence of a positive reaction to serological tests (the Sabin-Feldman dye test and the complement fixation test) must be evaluated with caution, since Toxoplasma antibodies are encountered in a large proportion of the normal population of urban and rural areas, the incidence increasing to 50% or more with increasing age.[52] Thus, to establish the diagnosis requires during the active phase of toxoplasmic infection a rising titer or significant differences in titer or histological evidence of Toxoplasma. This is illustrated by two studies recently published in Germany, in which Mutschler [53] considered he found toxoplasmosis to be the cause of a large number of neurological conditions (50 cases) and Kautzky [54] found

# References 46 and 47.

positive serological reactions for Toxoplasma in patients with neurological manifestations of varying origin (including cerebral tumor), in which toxoplasmosis could not, of course, play any part.

*Histoplasmosis.*—The conspicuous lesions of histoplasmosis are in the reticuloendothelial system, thereby focusing attention on the liver, spleen, lymph nodes, and lung. Of 120 cases reviewed, Schulz [51] found involvement of the central nervous system in 10%. In several of the cases the inflammation was confined to or most marked at the base of the brain, as in tuberculous meningitis.

Israel and his co-workers,[55] among others, have pointed out the histological resemblance between histoplasmosis and sarcoidosis.

*Infectious Mononucleosis (Glandular Fever).*—The anginose, or pharyngeal, variety generally presents no problem in differential diagnosis. The lymphatic type, which is characterized by generalized lymphadenopathy and mild fever, may, on the other hand, be confused with sarcoidosis.

Splenomegaly is often present. Hepatomegaly is not uncommon. Conjunctivitis has been noted. Neurological complications are comparatively common. In Thomsen's [56] series of 549 cases of infectious mononucleosis, involvement of the nervous system was recorded in 9%. Prominent features are pleocytosis in the CSF, mild meningitis, and/or encephalitis. Optic neuritis, ophthalmoplegia, ocular and facial paralyses, and polyneuritis have been described.[57] There are no reports of involvement of the lungs or skeletal bones or of uveitis. The febrile phase generally lasts from one to two weeks. The neurological symptoms sometimes persist for long periods and in the presence of irreversible damage may be permanent. The diagnosis is made by blood culture and the Paul-Bunnell test.

*Brucellosis (Undulant Fever).*—Brucellosis frequently runs a prolonged, sluggish course, characterized by intermittent fever of moderate degree and evidence of involvement of various organs and organic systems, especially manifested by lymphadenitis, arthritis, coronary changes, and enlarged spleen. An excruciating type of pain over the course of the sciatic nerve is encountered.[58] Other neurological complications appear to be comparatively rare. Meningoencephalitis and polyradiculitis would seem to be the commonest. Encephalomyelitis and ocular complaints, such as uveitis, retinal hemorrhage, and optic atrophy, are less common. An interesting feature is the long latent period between the onset of the disease and the appearance of symptoms, which period is not necessarily associated with a febrile episode.

Werner [59] states that undulant fever should be considered a possible cause in any case of meningoencephalitis showing a marked pleocytosis and high protein in the CSF.

*Behcet's Syndrome (Periadenitis Mucosa Necrotica Recurrens).*—Behcet's syndrome is a chronic recurrent vesicular affection of the mouth, genitalia, and, in many cases, the conjunctiva. It is sometimes combined with erythema nodosum. Neurological manifestations may occur in the presence of disseminated lesions in the brain and spinal cord. Recurrent meningoencephalomyelitis has been described.[60]

*Other Diseases Considered in Differential Diagnosis.*—Franke [61] and Silfverskiöld [62] have described retinal periphlebitis with recurrent hemorrhage into the vitreous humor, followed by paraplegia and pleocytosis in the CSF. The cases

described are very alike and may represent a separate syndrome of undetermined etiology. A possible relation of this condition to disseminated sclerosis has been suggested.*

The above survey of differential diagnoses makes no claim to be complete.

SUMMARY

Involvement of the nervous system in cases of sarcoidosis is considered to be comparatively rare, occurring in 1 to 5% of all cases. The incidence is probably somewhat higher if cases which lack clinical manifestations but exhibit slight abnormalities in the cerebrospinal fluid are taken into account.

The disease may involve any part of the nervous system. Facial paresis is one of the commonest signs and often is recurrent. The central nervous system may develop encephalitis, meningitis, or encephalomyelitis or may exhibit localized infiltration by sarcoid lesions, predominantly in the basal structures of the brain. These conditions may be manifested clinically by generalized or focal disturbances of cerebral function. Diabetes insipidus, arising from invasion of the pituitary gland, is not uncommon.

A report is given of nine cases of sarcoidosis with manifestations of nervous system involvement.

In seven of the patients neurological symptoms constituted the initial complaint. Of special interest are two patients who exhibited a picture of cerebral tumor. In one of them there was fairly rapid clinical regression of the symptoms, confirmed by the encephalogram. The other had a granulomatous, tumor-like mass arising in the choroid plexus and blocking the inferior horn of the right lateral ventricle, necessitating surgical intervention.

Ocular lesions were present in five patients, in three of them in the form of uveitis. A perusal of the literature shows that the incidence of uveitis is four times as frequent in patients with as in patients without signs of nervous system involvement.

The patients in the present series were followed for an average period of five years, during which the neurological symptoms either disappeared completely or showed marked regression. One patient died during this period of intermediate diseases.

Reports in the literature show that, although the prognosis in sarcoidosis is usually good, it is comparatively poor in patients with symptoms of nervous system involvement.

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# LAMINAR CORTICAL BLOCKING AND ITS RELATION TO EPISODIC AGGRESSIVE OUTBURSTS

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IN A PREVIOUS report evidence was presented to the effect that the EEG response pattern evoked by auditory stimulation during sleep in man is characteristically distorted in the presence of organic brain pathology. Two factors may play a role in the determination of the characteristics of the response pattern: (1) the presence of organic cortical damage and (2) changes in cortical excitability.

We are now reporting observations on an abnormal response pattern evoked by auditory stimulation during sleep in patients with episodic psychopathic behavior, in whom it may be inferred that the second factor, that of transient change of cortical excitability of a functional nature, is primarily at play. Experimental data in support of this assumption will be presented in this report.

## CLINICAL EEG STUDIES

The normal response pattern evoked by auditory stimulation during sleep in man, as revealed by scalp-to-ear EEG recording, consists of two components: (1) a slow-wave component consisting of a high voltage biphasic sway and (2) a fast component that consists of a train of 14-per-second biphasic sinusoidal oscillations (Fig. 1*A*).

In normal controls the response is synchronous and symmetrical in the homologous areas of the two hemispheres except for the temporal-occipital region, where some asymmetries of the slow component may occur physiologically. In patients with brain damage the response is distorted to a less or greater degree depending on the extent and severity of the underlying pathological process. The change involves both the slow and the fast component, and it consists chiefly of a reduction of amplitude (Fig. 1*B*).

In contrast to the latter pattern, found in patients with organic brain damage, response patterns to auditory stimulation during sleep, found in some patients with a history of episodic abnormal behavior (rage reactions, assaultiveness), show changes involving primarily the fast component. There is a loss of the characteristic biphas-

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icity of the 14-per-second waves with an accentuation of the positive phase (Fig. 2). Closer analysis of the potentials reveals that, although the negative phases are very much reduced or absent, the two other characteristics of the fast component, the 14-per-second frequency and the waxing-and-waning phenomenon, persist. It should be noted that the remaining positive phases show accentuation and sharp, spiky contours. The positive-wave response is a transient phenomenon, occasionally shifting

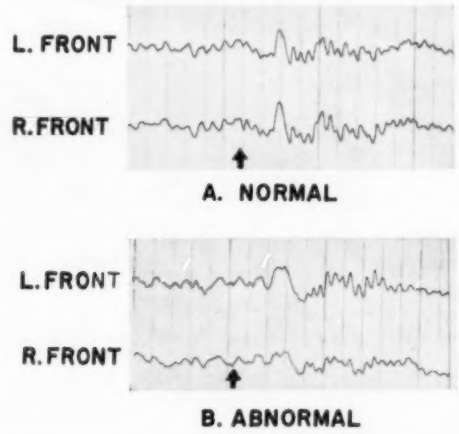


Fig. 1.—Electroencephalographic response of the human brain to auditory stimulation during sleep. *A*, response of normal brain; *B*, response of brain with organic lesion in the right frontal lobe. Arrow indicates time of application of auditory stimulus (1,000 cps).

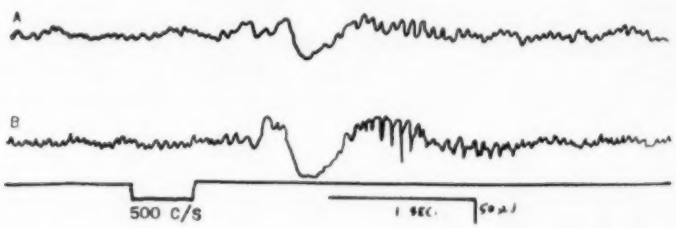


Fig. 2.—Electroencephalographic response of the brain of W. B., aged 19, to auditory stimulation during sleep. *A*, biphasic 14-per-second waves (L. midtemporal); *B*, positive 14-per-second "spikes" (R. midtemporal).

from one hemisphere to the other. In contrast, the response described in patients with organic disorder is constant and is confined to the side and the site of the affected hemisphere. Figure 3 shows a record in which positive-wave responses followed after every stimulus. This patient went into a typical rage reaction after he was awakened by a very loud stimulus. Weaker stimuli were able to shift the sleep activity from a deeper to a lighter stage with a repeated display of positive waves and immediate return to normal sleep activity. Frequently bursts of positive

waves appeared spontaneously, usually in the same leads. The spontaneous bursts could be distinguished from the evoked ones by the absence of the slow-wave component. Such spontaneous bursts are shown in Figure 4. They have all the characteristics of the evoked potentials except for the slow-wave component. Their frequency is often reduced to 6 or 7 per second, appearing occasionally, as in Figure 4, simultaneously with the 14-per-second waves, suggesting their close relationship. Whether evoked or spontaneous, the positive bursts are most clearly displayed in the posterior portions of the hemispheres (temporal-parietal-occipital).

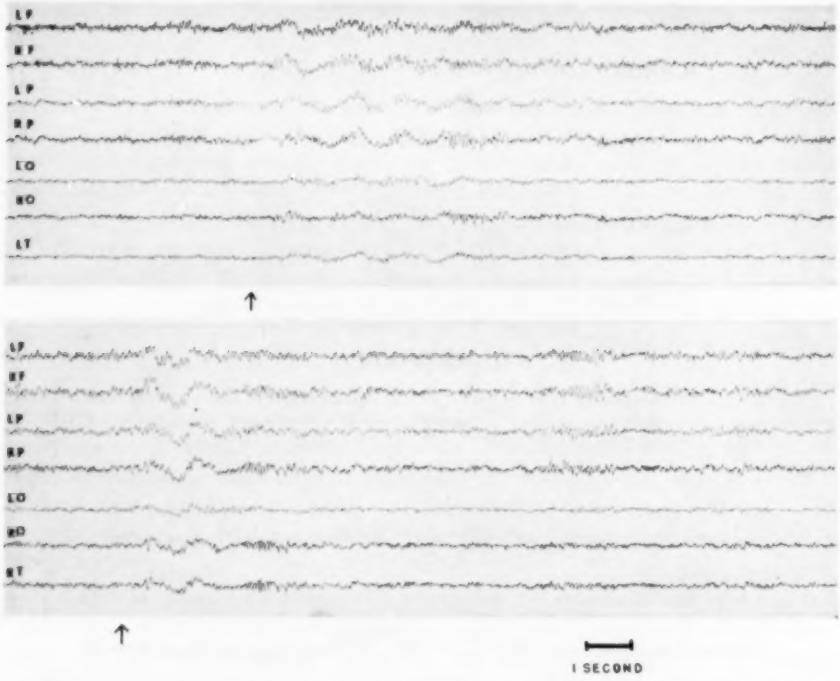


Fig. 3.—Sleep record. Lower tracing is a continuation of the upper. Arrows indicate the instant of application of auditory stimulus.

*Comment.*—The EEG response to an auditory stimulus during sleep, as described above, together with its pathological variants, should be distinguished from the primary response to auditory stimulation. The latter is a potential change due to the discharge of cortical cells in a very limited area of the cortex, namely, the auditory cortex. It has a short latency (ca. 10 msec.) and duration (ca. 60 msec.) and cannot be detected in the human with conventional methods from scalp electrodes. The primary response is carried by the specific auditory pathways from the cochlea via the medial geniculate body to Heschl's gyrus. The other response which we have discussed is a generalized response, appearing simultaneously and diffusely over the cortex of both hemispheres. It has a long latency (50 to 75 msec.) and is of long

duration (1 or 2 seconds) and should probably be considered as a diffuse after-discharge of cortical neurons activated by impulses reaching the cortex via the nonspecific diffuse thalamocortical system.

Changes in the response pattern of the diffuse after-discharge may theoretically depend on changes, structural or functional, at a cortical or subcortical level. The change seen in the response of patients with organic cortical damage involves both components of the response and may be accounted for by the more or less permanent loss of function of cortical neurons. This loss of function is caused by the organic process and is confined to the side and site of the lesion. The fluctuating character

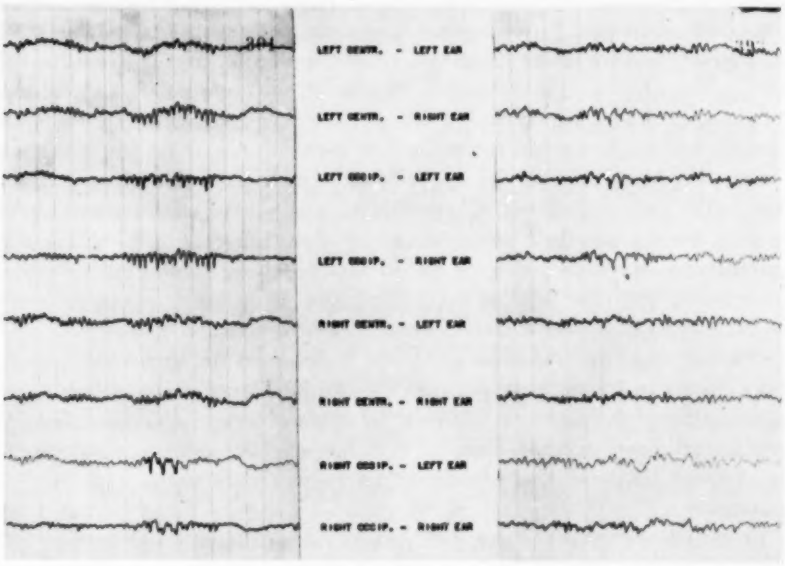

Fig. 4.—Spontaneous positive 7- and 14-per-second bursts recorded during sleep in a patient (W. B.) with "rage reactions."

of the abnormal pattern in the patients with episodic behavior, the shift of abnormal activity from one hemisphere to the other, and the lack of evidence of brain damage in the areas where these patterns are found suggest an impairment of a transient nature connected primarily with a pathophysiological disturbance rather than gross structural pathology.

As is evident from our findings, the positive waves not only were a part of the abnormal evoked response pattern but also appeared spontaneously or without evidence of external stimulation. This close relationship of the evoked activity to the spontaneous background activity is also evident in records of patients with organic brain pathology. Here the depression of the slow component of the response and the partial or complete lack of the fast component of the response are usually accompanied by a depression of voltage of the background slow-wave activity of sleep and a partial or complete lack of spontaneous spindles. This close relationship in patho-

logical conditions described here is found also in normal controls and was shown as early as 1939 by Davis and associates.[2] They observed: "The slow and the fast components of the K-complexes both resemble closely the delta waves and the fast waves which are characteristic of the spontaneous activity of the particular stage of sleep."

The spontaneous bursts of positive waves seen in the sleep records of our patients are identical with the "14 and 6 per second positive spikes" described by Gibbs and Gibbs [3] (1951). These authors found that in a significant number of persons with this EEG pattern a history of aggressive outbursts, such as episodic rage reactions and assaultiveness, could be found. Four patients of their series committed murder during a rage attack. Schwade and Geiger [4] (1953) have reported two other cases of homicide committed by youngsters whose sleep electroencephalograms showed characteristic positive bursts. Seventy-eight per cent of the cases described by Gibbs and Gibbs were in the 0 to 29 year age bracket. They classified the 14- and 6-per-second waves as an epileptic pattern because they correlated with epileptic types of clinical disorder, although the potentials were not considered to be, strictly speaking, a seizure discharge. As for the origin of these waves, the clinical manifestations suggested to them a thalamic or hypothalamic origin. The close relationship with the sleep spindles and the recent observations of the influence of the thalamus and hypothalamus on spindle activity in the cat have been suggested as further evidence for such an origin. The positive electrical sign so characteristic of this pattern has also been taken as further evidence of deep, subcortical origin.

However suggestive the above-mentioned implications are, we felt that the origin of the change in the biphasicity of the spindles is of greater significance for our understanding of the positive spikes than the origin of the spindles themselves. We, therefore, attempted experimentally to try to influence the cortex by topical application of drugs and to observe whether by such a procedure biphasic spindles could be changed.

In our experience with the animal cortex, such a change could be observed in circumstances that were suggestive neither of a convulsive state nor of involvement of the subcortex. Rather, it was observed in circumstances of depression of activity, such as in very deep barbiturate narcosis, exposure and drying of the cortex, and low blood pressure, as a permanent feature of the electrical activity of the cortex. Our aim was to find out how a transient change can be achieved.

## EXPERIMENTAL RESULTS

Experiments were carried out on cats under diallylbarbituric acid (Dial) narcosis. Electrical activity was recorded with an eight-channel Grass electroencephalograph, using wick electrodes placed directly on the cortex. Both bipolar and monopolar recordings were made. In the latter instance the indifferent electrode, in the form of a suture needle electrode, was inserted into the ipsilateral inactive tissue (cut edge of scalp). After the dura was removed, a gyrus showing typical barbiturate spindles was chosen for the experiment. Recording was made (Fig. 5) from two areas of the chosen gyrus—the suprasylvian gyrus. One area (Area I) acted as a control; the other (Area II), at a distance of 4 mm., was treated with the drug.

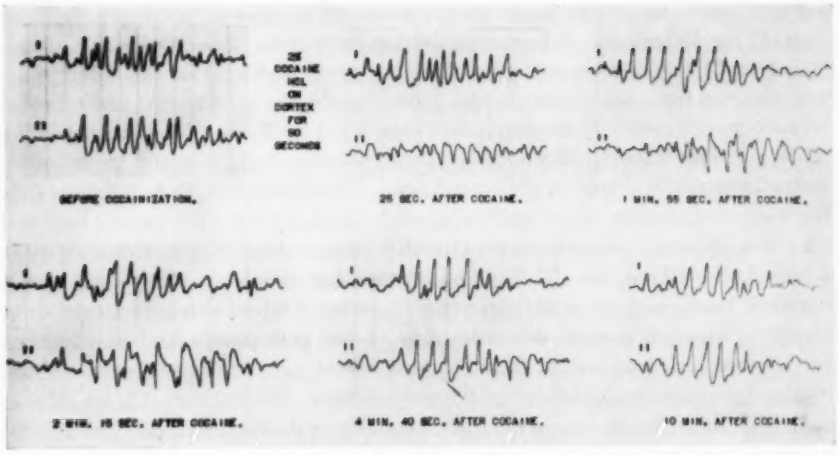
2% COCAINE HCL ON CORTEX FOR 90 SECONDS
BEFORE COCAINIZATION.
25 SEC. AFTER COCAINE.
1 MIN. 55 SEC. AFTER COCAINE.
2 MIN. 15 SEC. AFTER COCAINE.
4 MIN. 40 SEC. AFTER COCAINE.
10 MIN. AFTER COCAINE.

Fig. 5.—Influence of local cocainization on "spindle" activity of cat under diallylbarbituric acid (Dial) narcosis (suprasylvian gyrus). *I*, control area; *II*, cocainized area.

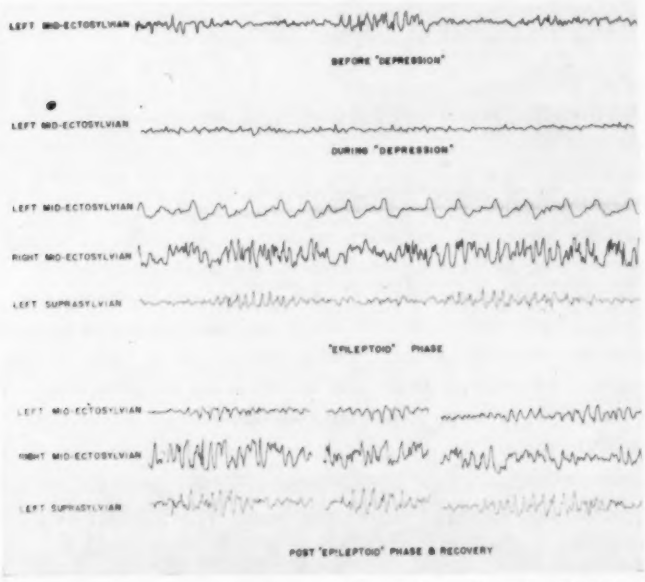


Fig. 6.—Electrocorticogram recorded from a kitten 3½ months old. Diallylbarbituric acid anesthesia. Spontaneous "spindles" during a cycle of "spreading depression" of the epileptiform type.

Figure 6 shows a typical sequence of electrical events occurring in these areas when a 2 by 2 mm. piece of filter paper soaked with a 2% cocaine solution was placed on Area II for 50 seconds. Before cocainization, both areas showed trains of normal spindles. Twenty-five seconds after the filter paper with cocaine was removed, it was observed that a significant change occurred in the electrical tracing of the treated area when compared with the untreated (control) area. There was definite abolition of the previously outstanding negative phase of the potentials in the treated area, with no observable change in the control area. The treated area showed a most conspicuous exaggeration of the positive phases, which became even more prominent after two minutes. Complete recovery with a reappearance of normal spindles was achieved after 10 minutes. It should be stressed that in order to bring about such a sequence heavy soaking of the filter paper and too long an exposure to the drug should be avoided. Longer exposures may abolish both phases, and an irregular, very slow activity may result. Only a superficial and short-lasting penetration of the cocaine solution is apt to bring out the positive-burst phenomenon. The same phenomenon can be brought out with application of pentobarbital sodium (Nembutal).

Bursts of positive spindles could also be observed during the so-called "spreading depression" of Lēao * (1944 and 1945), especially during the stage following the "epileptoid" phase. This is illustrated in Figure 6.

In the two upper tracings the electrical activity of the left midectosylvian gyrus is shown before and during depression. The normal spindle bursts recorded before the depression are blanketed when the wave of spreading depression reaches the gyrus. During the following "epileptoid" phase, high-voltage paroxysmal slow waves are recorded from the gyrus, a very localized event, as can be seen from the unchanged activity recorded simultaneously from the adjacent left suprasylvian and the homologous contralateral right midectosylvian gyrus. After the paroxysm is over, the electrical activity begins to reappear first with monophasic positive bursts, the biphasic activity appearing later when recovery is complete. (The importance of monopolar recording in these experiments cannot be overemphasized. Only when recording is made with reference to an "inactive" lead can the true polarity be established. If recording is made from both electrodes placed on active tissue, the resultant phase of the potentials is not a true picture of either area. When, however, disappearance of the negative phase and its return are recorded from a monopolar lead, it is reasonable to assume that the recorded change occurs under the active electrode only.)

*Comment.*—As shown above, spindle activity can be changed into positive bursts by the superficial application of depressant drugs. The fact that only a superficial and a short-lasting application is apt to bring out this phenomenon suggests that the monophasic positive burst is a result of a laminar blocking action of the drug on neural structures in the rather superficial layers of the cortex. This assumption is in general agreement with that of other investigators: McCulloch * (1949), who showed that after laminar thermocoagulation, killing the outer layers of the cortex, the surface positive phase of the strychnine spike remains, but the subsequent surface

* References 5 through 7.

negative phase is gone; Chang [9] (1951), who studied the blocking effects of procaine hydrochloride on the response following direct electrical stimulation of the cortex, and Arduini and Terzuolo [10] (1951), who studied the same effect on the recruited potentials evoked by stimulation. Chang in his study brought forward evidence that the penetration of procaine hydrochloride into the superficial layers blocks the negative phase component of the potential.

Arduini and Terzuolo found that the negative recruited potentials were constantly reversed in sign by local application of 5% cocaine on the surface, and their evidence suggests that the negative waves are a result of activation of cortical cells. They further stated that the positive waves "were not related to physical spread of bioelectric potentials from subcortical regions, since after undercutting the underlying white matter only the stimulus artifact is observed in the cortical record."

It is, therefore, obvious that all the evidence from studies made on the effects of laminar thermocoagulation, on the blocking effect of cocaine on the direct response to electrical stimuli, on the recruited responses, and, in our studies, on the "spindles" points to a cortical rather than a subcortical mechanism and that a blocking of cortical activity plays a significant role in the production of the electrical pattern of positive bursts. The possible, though disputed, implication that cortical spindles originate from or are influenced by the thalamus or the hypothalamus has in our interpretation no bearing on the problem of the mechanism of the positive bursts. The problem here is that of the change in the spindles, where and how this occurs. The evidence shown above indicates that the change, or reduction of the negative phases of the potentials, is most likely produced by an intracortical blocking, and not by thalamic or hypothalamic excessive neuronal discharge.

There is further evidence that conditions of a general nature, usually regarded as causing depression of cortical activity, are apt to bring out "positive burst" patterns. These are increased depth of barbiturate narcosis, cooling or drying of exposed cortex, lowering of blood pressure, and anoxia. It is of special interest to mention here Bremer's [11] (1949) observation:

> When the brain is in a condition of moderate functional depression, the positive wave [of the biphasic response] is paradoxically increased (apparently by disocclusion), the negative component is absent, and the fast after-discharge is replaced by a series of surface-positive waves.

This was a finding which we were able to confirm.

## GENERAL COMMENT

Our EEG observations confirm the original findings of Gibbs and Gibbs that the 14- and 6-per-second spikes present a characteristic electrical pattern, which, if fully developed, can be distinguished from normal electrical potentials. We prefer, however, to use the term positive bursts, as it is less committal, since there is a natural tendency of the clinical electroencephalographer to regard spikes as a characteristically epileptic pattern.

The fact that the positive bursts occur in patients with overt epilepsy or in patients with other manifestations of a paroxysmal nature does not in itself assure that these bursts are true epileptic potentials due to an excessive neuronal discharge. The evidence that abolition of the negative component of spindle activity with resultant positive bursts can be produced experimentally by depression or neural

elements in the superficial layers of the cortex suggests another possible explanation. It indicates, in all probability, that the mechanism at play here may be that of a transient depression or blocking of cortical structures rather than an excessive neuronal discharge in subcortical nuclei. Such an interpretation not only would be in conformity with the experimental evidence presented above but would also much better account for the clinical manifestations seen in subjects who consistently show positive bursts in their electroencephalograms.

The topographical distribution of the positive bursts in the posterior temporo-parieto-occipital regions should also be given consideration. This important posterior association region is late in development ontogenetically (Turner,[12] 1948). Finally, the fact that the positive bursts are seen mostly in the younger groups suggests a factor of immaturity.

As shown by Gibbs and Gibbs, the clinical correlates drawn from a large number of cases point to a significant relationship between positive bursts and episodic abnormal behavior, like rage reactions and assaultiveness, resulting in some instances in homicide. The assaultiveness of patients with this EEG pattern is described to be "precisely directed and skillfully executed," as distinguished from the behavior of patients during a psychomotor seizure. All patients in the group of Schwade and Geiger [4] presented a history of sudden outbursts of violent behavior. This behavior varied from sudden outbursts of rage with destruction of objects in the environment to the extreme of murder or attempted murder or mutilation.

The patient with positive bursts who shows highly coordinated and precise motor activity during an episode of abnormal aggressive behavior must be considered to have a disturbance of a more subtle nature. The electroencephalographic findings in these patients, especially during sleep and under the stress of an arousal stimulus, point toward instability of the superficial layers of the posterior temporo-parieto-occipital association cortex. As shown above (Fig. 3), the activation of the cortex in such a subject during arousal produces normal biphasic oscillations over all cortical areas except the mentioned association regions. There, a loss of the negative phase of the electrical output produces monophasic positive waves. The disturbance under these circumstances should be regarded as a faulty return to normal wakeful activity of this subject's cortical association areas. It is conceivable that rage or aggressive abnormal behavior may occur in these persons in circumstances other than arousal from sleep if conditions are present that are apt to evoke a transient blocking of the centers of highest integration of cortical activity. Whether environmental stress in these persons is able to produce blocking of the association areas is of interest, but beyond the scope of this paper. The coordinated abnormal behavior during such an episode becomes more comprehensible if we regard such a patient as acting under a condition of a very selective partial "laminar decortication." It is possible that there is a loss of higher cortical inhibitory mechanisms, with a consequent release of primitive aggressive reactions. Excessive discharges of subcortical nuclei and autonomic manifestations seen in these persons may be explained as release phenomena rather than as caused by a thalamic or hypothalamic epileptogenic focus.

The topographical distribution of positive bursts and its connection with abnormal behavior raises the question of its relationship with disturbances of the posterior

temporal cortex described by other workers. That temporal lobe dysfunction may be responsible for some mental disturbances (hallucinations, dreamy states, amnesias, etc.) is now well recognized and needs no elaboration here. However, the demonstration of the connection of symptoms like aggressiveness and irritability with EEG disturbances of the posterior part of the temporal lobe is rather recent. Hill and Watterson [13] (1942) and Hill [14] (1944) reported temporal lobe EEG abnormalities in a group of aggressive psychopaths. Rey and associates [15] (1949) and Hill [16] (1952) reported EEG abnormalities in the posterior portion of the temporal lobe associated with abnormal behavior. The factor of immaturity is considered by these authors to be of significance. The topography of the EEG abnormalities, the symptoms, and the age bracket of our patients would suggest some relationship with patients studied by these authors. However, the characteristic positive bursts were never found by these authors,† a fact which may be attributed to the technique (bipolar) used by the British workers and the omission of sleep and stimulation methods.

The problem as to whether the behavior disturbances in this young age group are due to an epileptic discharge in the subcortex or to a transient blocking in the immature outer layers of the sensory association cortex is of more than academic interest. The diagnosis of epilepsy in a patient with episodic abnormal behavior should probably not be made if the only abnormal EEG finding is that of positive bursts. Rather, the question of a delayed maturity should be entertained and the prognosis and handling of the patient adjusted accordingly.

It may be of interest to mention here the fact that a stimulant, like amphetamine, is remarkably successful in certain cases of behavior disorder in children, whereas a depressant like phenobarbital, may exaggerate symptoms (Cutts and Jasper,[17] 1939) and is contraindicated in such cases (Lindsley and Henry, [18] 1942). This paradoxical action of the depressant on some behavior disturbances usually accompanied by hypermobility may possibly be related to the assumption postulated in this paper, i. e., that some abnormal behavior is due to depression of the cortex and a depressant drug may, therefore, aggravate the condition.

Finally, the implication that epilepsy is responsible for the state during which some criminal acts are performed (the positive waves have been labeled "murder waves") may add a new social stigma to the already heavily stigmatized epileptic. Even without the above-mentioned findings, it is felt by many authors that purposive behavior, such as that involved in a murder, cannot be carried out in a true epileptic seizure. In the light of our experimental findings, transient cortical blocking seems to be a more workable hypothesis, related to both the phenomenology of the disturbance and its electrical correlates.

SUMMARY

Experimental studies of the EEG during sleep reveal two types of abnormal EEG responses to auditory stimulation: one, found in patients with organic brain damage, is confined to the side and the site of the lesion; the other, found in some persons with episodic aggressive behavior, is confined to the association cortex of posterior parts of the hemispheres.

† Hill, D.: Personal communication, 1952.

The second type of response is characterized by positive bursts that replace the normally occurring biphasic bursts. These evoked bursts are identical with the spontaneously occurring "positive 6- and 14-per-second spikes" observed by Gibbs and Gibbs.

Results obtained by experimental methods showed that positive bursts similar to those seen in the human are reproducible in the animal cortex by blocking of activity of the cortex by topical application of depressant drugs. Positive bursts are also seen during the recovery cycle of "spreading depression" of Lĕao and in general conditions of depression of cortical activity, like deep anesthesia, low blood pressure, and anoxia.

It is inferred that positive bursts in the human EEG, evoked or occurring spontaneously during sleep, are sleep spindles whose negative phase has been reduced or abolished. This may be due to blocking of activity in the superficial layers of the association cortex in the posterior temporo-parieto-occipital region. The high incidence of positive bursts in the younger age bracket suggests that delayed maturation of this region may play a role in the production of the electrical abnormalities and clinical manifestations.

The hypothesis that clinical manifestations (rage, assaultiveness, and accompanying autonomic changes) are release phenomena due to transient laminar blocking of inhibitory mechanisms in the superficial layers of the association cortex is discussed.

Dr. Alden Broward aided in the preparation of the manuscript.

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# SPINAL CORD COMPRESSION STUDIES

## III. Time Limits for Recovery After Gradual Compression in Dogs

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IT IS HARDLY necessary to justify an experimental study in medicine aimed at providing more precise information under more controlled conditions than can be supplied by what Hughlings Jackson called "Nature's experiments." The purpose of accumulating such experimental, not to mention clinical, data is to enable one to foretell events in given circumstances. The ultimate end of this scientific approach is to understand the course of a disease process and to attempt to control it.

Of course, the results of animal experiments are not always directly applicable to man because of anatomical, physiological, and biochemical differences among species. It remains true, nonetheless, that man has often been the beneficiary of critically evaluated experiments carried out on animals.

In this investigation, by the use of techniques for producing gradual spinal compression described previously,[6] we have studied the recoverability of spinal cord function in dogs that, in varying lengths of time, became completely paralyzed and remained so for equally varying times. We also studied the sequence of loss and recovery of sensory and motor functions in these animals.

The gradual compression device [6] consists of a fixed-speed motor attached to a shaft that turns a screw compressing a bellows. The liquid in the bellows is forced through a tubing into a rubber balloon introduced into the midthoracic region through a small laminectomy opening at $T_{12}$. The tubing is fixed to the skin with collodion, and the animal is housed in a circular cage just wide enough to allow forward and backward movement. The dog may be examined at any time during the period of progressive increase of sensory and motor function.

The first gradual compression device used was designed to inflate the balloon fully four hours after the motor was started, at which time complete paralysis below the compression site (midthoracic) was produced. However, there was no discernible evidence of spinal compression for the first half-hour that the motor ran. At the end of this time a pressure drop occurred in the manometer attached to the balloon, and roentgenograms showed that the balloon had reached a size approximately one-half of that of the spinal canal.

A few minutes later the animal became restless, growled, and resented examination. The dog was doubtless in pain. Weakness began about 45 minutes after the motor started, and usually in another hour the hindlimbs were completely paralyzed. Roentgenograms showed that the balloon filled the spinal canal one hour after the

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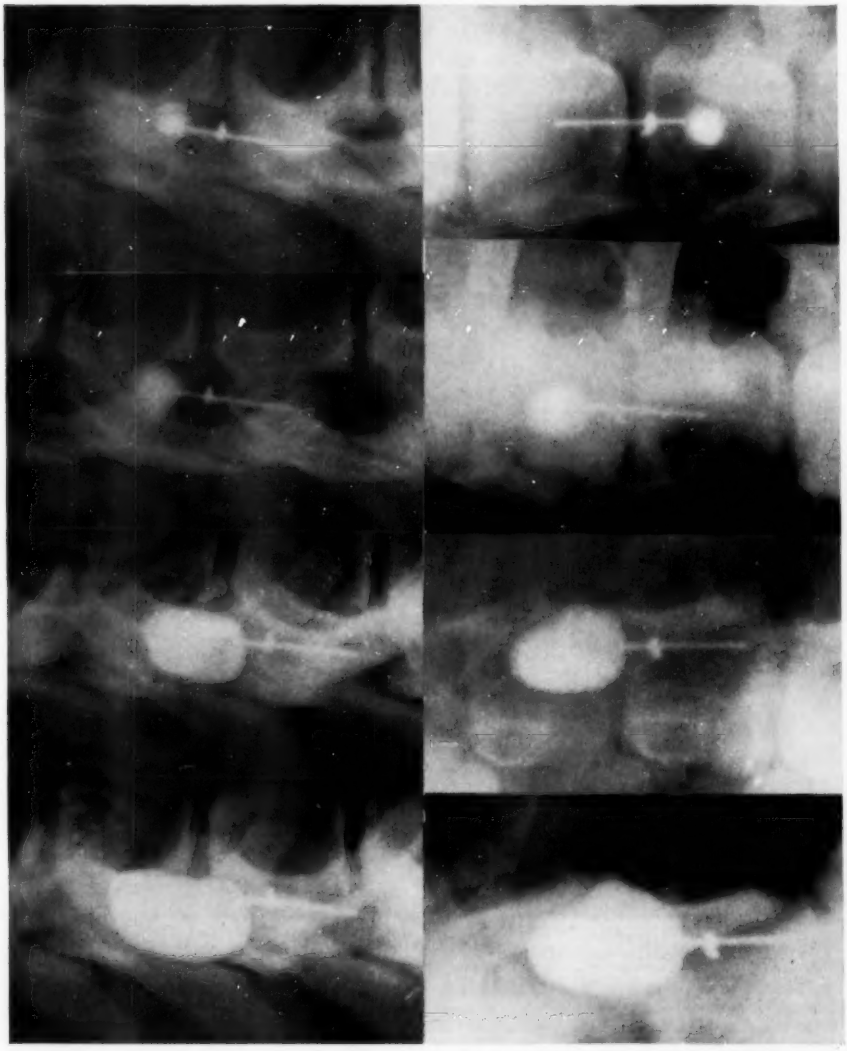

Fig. 1.—Lateral (left) and anteroposterior (right) roentgenograms, showing inflation of balloon over the course of three hours on the machine for gradual compression. The animal showed complete paralysis of hindlimbs after full inflation of the balloon, which was at the level of the seventh thoracic vertebra.

motor was started (Fig. 1). The actual time of spinal cord compression from the onset of pain to complete paralysis of the hindlimbs averaged 75 minutes. Observations of the same sort showed that the actual spinal compression times for the 3-day and the 1-week compressor units were approximately 20 hours and 48 hours, respectively.

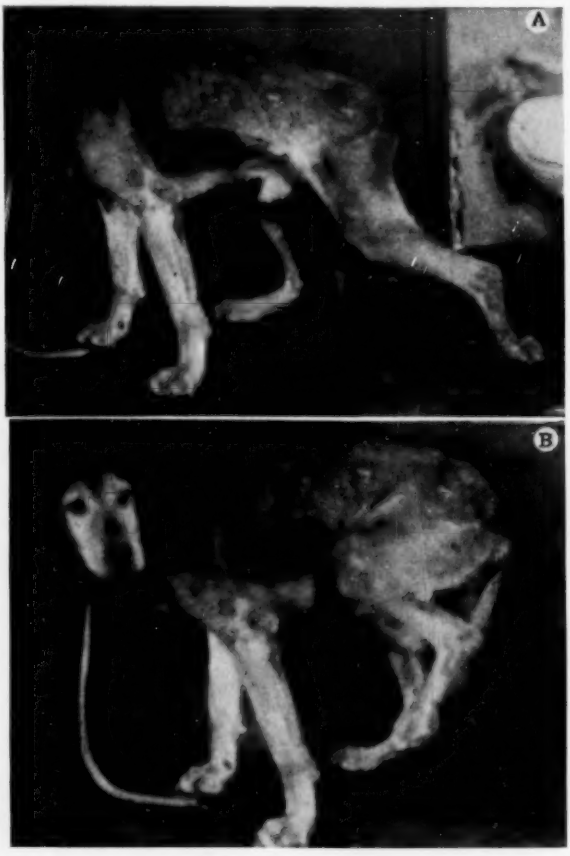


Fig. 2.—Photograph of dog showing *A*, loss of position sense of hindfoot, and *B*, prompt withdrawal of hindlimb upon pinprick stimulation of the foot.

This dog showed complete sensorimotor paralysis after a 10-hour period of gradually increasing compression of the midthoracic spinal cord. The compression was released immediately after the dog became completely paralyzed. The above photographs were taken six days later, when there was a normal pinprick response with lost position sense and touch sensation. Moderate return of motor power had occurred. Full sensorimotor recovery occurred approximately 150 days after decompression.

The techniques of operation and functional examination, as well as the methods of preparing the spinal cords for histologic study, were described in Parts I and II of this series of studies.*

* References 6 and 7.

*RECOVERY TIMES AFTER GRADUAL CORD COMPRESSION*

With increasing spinal compression it is quite apparent that motor power is usually lost before pinprick reaction is. Frequently we have observed that a dog may show complete hindlimb paralysis and yet respond to the application of a pinprick to the plantar surface of his paws. He will turn his head and look at the site of the prick, attempt to withdraw, or bark. Since tests of touch and position sense are dependent upon motor power, no conclusions could be drawn concerning the sequence of loss of these functions when the limb is weak or paralyzed. However, during the phase of functional recovery it is quite clear that motor power returns before position sense (Fig. 2).

TABLE 1.—*Gradual Spinal Cord Compression Occurring Over Period of Seventy-Five Minutes Leading to Complete Paralysis*

| Dog No. | Duration of Compression | Degree of Paralysis at Time of Killing | Interval, in Days, from Release of Compression to Time of Killing or Recovery | Histologic Results |
|---|---|---|---|---|
| 111 | Momentary | 0 | 19<br>Full recovery in 12 days | No histologic abnormality |
| 234 | 5 min. | 0 | 14<br>Full recovery in 4 days | No histologic abnormality |
| 197 | 3 hr. | 0 | 30<br>Full recovery in 17 days | Slight vacuolation at compression site; occasional chromatolytic ganglion cell in gray matter at compression site |
| 151 | 6 hr. | 0 | 107 | No histologic abnormality |
| 142 | 8 hr. | 0 | 178<br>Full recovery in 24 days | No histologic abnormality |
| 260 | 9 hr. | 0 | 72<br>Full recovery in 62 days | No histologic abnormality |
| 213 | 12 hr. | 100 | 18 | Almost total replacement of spinal cord tissue by fat-filled phagocytes—one ventral column less affected than other areas; nerve roots spared |
| 252 | 12 hr. | 100 | 111 | Gray matter cavitation but anterior horn cells normal for most part, at compression site; slight vacuolation of white matter |
| 146 | 12 hr. | 100 | 19 | Moderate rarefaction at compression site, most marked ventrally; more degeneration of myelin sheaths than axis cylinders |
| 206 | 24 hr. | 100 | 48 | Marked rarefaction at compression site where spinal cord tissue is largely replaced by fat-filled phagocytes; destruction, most marked dorsally, extends at least 3 spinal segments |

Table 1 shows that the dogs in which complete sensorimotor paralysis occurred over a 75-minute period of gradually increasing compression recovered fully if the compression was released within 9 hours, but not later. Recovery began in these dogs in from 1 to 13 days after release of compression and was complete in from 4 to 62 days.†

After a gradual increase in spinal compression leading to total paralysis, coming on over 20 hours, the safety period for recovery after decompression increases to 84 hours (Table 2). The dog (209) in which compression was maintained for 96 hours showed no recovery whatever during his 35-day survival period. In view

† The sequence of return of the different functions tested was not determined in this series of dogs.

TABLE 2.—*Gradual Spinal Cord Compression Occurring Over Period of Twenty Hours Leading to Complete Paralysis*

| Dog No. | Duration of Compression, in Hours | Degree of Paralysis at Time of Killing | Interval, in Days, from Release of Compression to Onset of Recovery | Interval, in Days, from Release of Compression to Time of Killing or Recovery | Histologic Results |
|---|---|---|---|---|---|
| 105 | Momentary | 0 | Pain recovery began in 2 days, complete in 4 days; motor recovery began in 4 days; complete recovery in 26 days, position sense recovery slowest | 92 | No histologic abnormality |
| 142 | 6-8 | 0 | 12-32 days<br>All functions recovered approximately simultaneously | 206<br>Dog reached full recovery in 169 days | No histologic abnormality |
| 200 | 51 | 0 | 28<br>Pain recovery was first | 119 | Lateral half spinal cord at compression site somewhat demyelinated, the other half being vacuolated; axones somewhat thinned in demyelinated half; ganglion cells normal at compression site |
| 156 | 72 | Recovery, then relapse 100 | Recovery of all functions began in 6 days; recovery almost complete in 10 days, and then animal appeared ill and relapsed | 47 | Moderate vacuolation at compression site; moderate reduction of nerve fibers at compression site seen in Gros-Bielschowsky and Weigert-Pal preparations; thinning of nerve fibers confined to lateral white columns; some reduction of nerve cells at this level |
| 195 | 72 | 0 | 17<br>Pain and motor power recovered first | 128 | No histologic abnormality |
| 100 | 84 | 0 | Pain recovery complete in 6 days when motor recovery began; full recovery of all functions except position sense in 25 days; position sense recovery, 157 days | 157 | No histologic abnormality |
| 209 | 96 | 100 | ..... | 35 | Marked rarefaction at compression site, where spinal cord tissue is largely replaced by fat-filled phagocytes |
| 59 | 96 | 100 | ..... | 36 | Marked rarefaction at compression site |

of the marked destruction of the spinal cord observed histologically in this dog, he could not have recovered even if he had survived longer. Dog 59, with compression for the same time interval, also showed severe cord destruction.

Further extension of this therapeutic safety period occurred in dogs increasingly incapacitated to the point of total paralysis over a 48-hour period of time. The

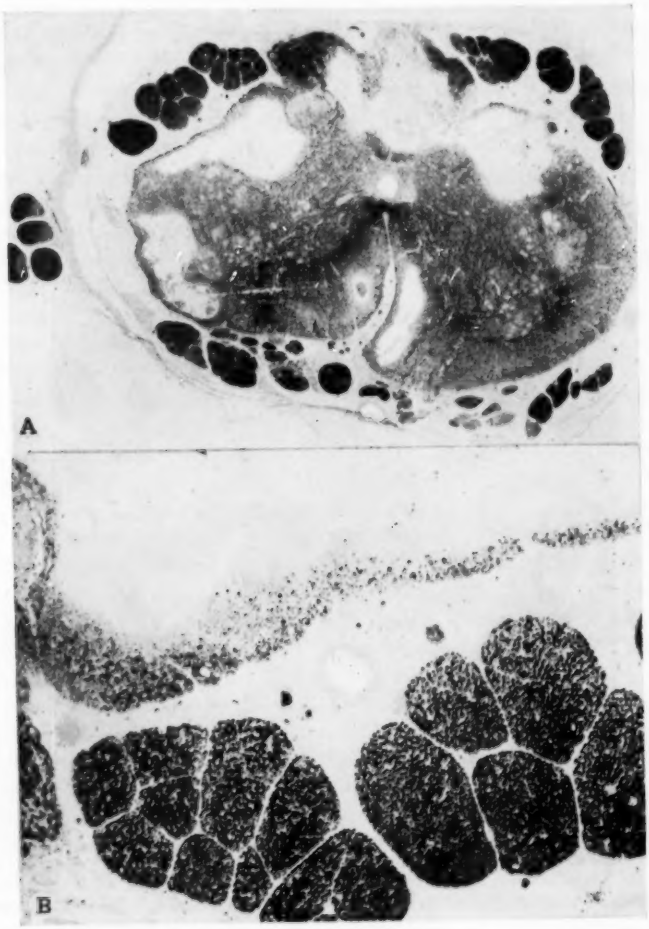


Fig. 3.—Photomicrographs taken from $L_4$ spinal segment at site of gradually increasing compression over 25 hours leading to complete paralysis. Compression was maintained for 12 hours. There was full functional recovery. Note the extensive degeneration of the conus medullaris at the compression site. The nerve roots are normal.

Weigert-Pal preparations for myelin sheaths; *A*, × 11; *B*, × 67.

critical time limit in this series was one week, beyond which the paralysis was irreversible. In this series there was the same sequence of sensory and motor recovery as occurred in the majority of dogs in the 20-hour series.

In most of the dogs pain sensation returned first, and in three animals it was normal in four and six days after spinal compression. Motor recovery began in from 4 to 10 days and was complete in no more than 25 and 26 days in two dogs. The time limits for full recovery of function varied from 24 to 157 days (Tables 1 and 2). Position sense returned most slowly.

There was a tendency toward a direct relationship between the onset and consummation of recovery, on the one hand, and the duration of the spinal compression, on the other, but exceptions to this rule did occur. Variations in the health of the dogs and in the exact position of the balloon in the spinal canal probably

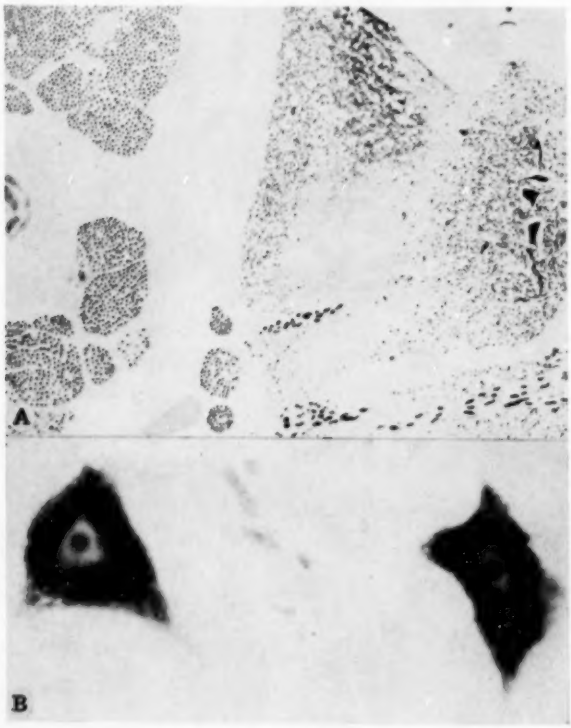


Fig. 4.—Photomicrographs taken from the compression site of the same animal from which the sections shown in Figure 3 were taken. The greater resistance of the axones of the nerve root than of the spinal cord axones is clearly shown. The ganglion cells, *B*, are normal.

*A*, Gros-Bielschowsky impregnation for axis cylinders, × 67; *B*, toluidine blue stain, × 593.

accounted, in part at least, for inconsistency in the results. The effect of the animal's health upon recovery was well illustrated by Dog 156, which after it had recovered almost completely became listless and emaciated and relapsed to a state of complete paralysis.

In the animals that recovered function, histologic studies showed either no abnormality or slight vacuolation or rarefaction at the compression site. In one of these dogs there was a cavity in the white matter about the size of the ventral gray horn. In the dogs that did not recover, the histologic changes varied from moderate

rarefaction of nerve fibers to complete softening or cavitation at the compression site (Fig. 3). There was no evidence of a greater effect on the ganglion cells or of a greater effect on the gray than on the white matter of the spinal cord (Fig. 4), nor were there any consistent differences in vulnerability of myelin sheaths or axis cylinders at the compression site.

## COMMENT

Early in the course of this study we produced cauda equina compression, planning to compare this structure and the spinal cord in their relative compression vulnerabilities. Dogs gradually paralyzed by compressing the cauda equina over a period of 24 hours fully recovered when the compression was maintained for as long as 77 hours. However, in some animals histologic studies showed hemorrhage in the conus medullaris, ascending to the part of the spinal cord innervating the hindlimbs. Because of the variation in functional and histologic effects produced by cauda equina compression, we did not complete this series. It is clear, however, from our previous studies on acute compression, and also from our electrophysiological studies now in progress, that the cauda equina can withstand considerably more pressure than the spinal cord (Fig. 3).

The area of maximal histologic change after spinal cord compression varies considerably, and there is no one part of the spinal cord that appears to be more vulnerable than any other. The nerve roots, however, are much more resistant to compression than the spinal cord. Nowhere in the cord is there an area containing nerve fibers of only a single fiber thickness. On the contrary, there is such intermingling of nerve fibers of various sizes in different parts of the spinal cord that one cannot determine histologically whether one fiber size is more vulnerable to compression than another. There is no doubt, however, from our functional observations that the fibers conveying pain sensation are much less vulnerable than those conveying motor and position sense impulses.

The possibility that the pain response in our dogs resulted from impulses passing upward along pathways of the sympathetic nervous system is excluded by the fact that in every instance it was possible to abolish this response by increased spinal cord compression.

Our studies have clearly established the fact that dogs usually lose motor power and position sense before they lose pinprick reaction. Dogs with such compression are the experimental counterpart of clinical cases of spinal cord compressions masquerading as posterolateral sclerosis or amyotrophic lateral sclerosis. I removed a posterior spinal cord tumor from a totally paralyzed woman who had lost posterior-column sensation but had normal pinprick appreciation. From another severely quadriparetic woman who showed no sensory abnormalities I removed a ventrally placed meningioma. Both patients made splendid recoveries and were able to walk unsupported after operation.

These cases point up the importance of being aware of the fact that the large-fibered pyramidal tract and posterior columns are more vulnerable than the finer fibers, conveying pinprick sensation. Kahn [4] and others have stressed the clinical importance of this phenomenon. Although Kahn has pointed out that the amyotrophic lateral sclerosis syndrome is produced by anterior spinal cord compression, dogs whose spinal cords were compressed dorsally and laterally, as well as ventrally, have shown severe and even total paralysis, with a good response to pinprick stimulation of the paralyzed extremities.

Gasser and Erlanger [1] have found that on compression of a peripheral nerve the nerve fibers are affected in the order of their size, the large fibers losing their conductivity first. Accordingly, motor, vibratory, and touch fibers lose their conductivity before pain fibers do.

Häggqvist [3] has shown ‡ that in the spinal cord of man the nerve fibers are roughly proportional in size to their corresponding peripheral nerve fibers, even though they become constricted, as I have previously shown,[5] in passing through the pial ring of the nerve root. Our present observation of preserved pinprick response in dogs after loss of motor power and position sense shows that the pain fibers in the spinal cord, like those in the peripheral nerve, are less vulnerable to compression than the motor and position sense fibers.

In anterior spinal cord compression, if the pressure were equally distributed, one would expect the same changes in conductivity as result from compression of a peripheral nerve. The same changes do not occur, however, and the production of the syndrome of lateral sclerosis by anterior compression is attributed by Kahn [4] to "the strong attachments of the dentate ligaments . . . [which] prevent this equal distribution of pressure." Stress on the pyramidal tract "almost as great as on the lateral spinothalamic is thus produced." Because of the larger size of the pyramidal tract fibers, they show more "disturbance of conductivity than the pain fibers of the spinothalamic tracts, even though the latter are closer to the compressing mass. . . . Touch is preserved because, even though the touch fibers of the ventral spinothalamic tracts may fail to conduct, there is still sufficient sensation carried in the more protected posterior columns to prevent the clinical detection of touch disturbance. Postural sense is preserved because the attachment of the dentate ligaments prevents the posterior columns, which are farthest from the compressing mass, from being pressed against the unyielding laminae. Thus may be produced a clinical, though not necessarily a pathological, picture of lateral sclerosis with pyramidal tract disturbance and little or no sensory change."

Kahn suggests that the "larger fibers with their greater irritability and their greater rate of conduction have higher metabolic requirements than the smaller fibers. They, therefore, more quickly reflect the metabolic disturbance caused by the ischemia of compression with its resultant anoxia."

On the basis of our studies it seems unlikely that ischemia is the main cause of spinal compression symptoms.[6] Experimental studies on the effect of asphyxia, ischemia, and anoxia show that there is a minimal latent interval of at least several minutes before even the most vulnerable spinal cord structures cease functioning.[2] Moreover, recovery from bouts of even total ischemia has been shown to begin in a few minutes.

On the other hand, the paralysis that followed acute compression of the spinal cord in our dogs was instantaneous, and recovery did not begin usually before 9 to 16 days after decompression. Recovery was delayed for even longer times in our dogs subjected to gradually increasing spinal compression. Moreover, the histologic changes in the spinal cords of dogs consisted of vacuolation, deformation, and cavitation. Some degeneration of ganglion cells occurred, but there was no predilection toward any histologic changes in the gray matter (Fig. 4). Anoxia,

‡ Häggqvist's studies are supported by our own unfinished ones on the distribution of nerve fiber sizes in the spinal cord of man, which probably corresponds roughly to that in the spinal cord of dogs.

on the other hand, affects primarily ganglion cells.[7] These facts emphasize the mechanical rather than the anoxic as the main factor in causing paralysis due to spinal compression. This concept is further emphasized by the fact that with compression it is possible to abolish all electrical activity instantly, although the compressive force is far short of transection.§ Moreover, if not maintained too long, such compression, when released, is compatible with recovery.

## CONCLUSIONS

1. Functional recovery after gradually increasing extradural compression of the spinal cord in dogs depends upon the length of time selected to produce the paralysis and upon the duration of the spinal cord compression.

2. Full recovery of function occurred after 75-minute periods of increasing and finally total paralysis when the compression was released within 9 hours after the onset of total paralysis, but not longer. This therapeutic safety period is increased to 84 hours and 1 week when the time during which total paralysis occurs is prolonged to 20 and 48 hours, respectively. The duration of spinal cord compression compatible with recovery increases, therefore, with prolongation of the time during which the paralysis develops.

3. With gradually increasing spinal compression in dogs, pain sensation persists after motor function of the hindlimbs is lost, and during the recovery phase it returns usually before motor power and position sense.

4. The main cause of paralysis after spinal cord compression is direct mechanical blockage rather than anoxia.

5. These studies support the clinical observation that patients harboring spinal cord tumors may show the picture of pyramidal tract disease alone or in combination with posterior column symptoms. Patients with these syndromes should, therefore, be carefully studied for signs of spinal cord compression.

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§ These are unpublished observations from our neurophysiology laboratory, under the direction of Dr. S. Gelfan.

# ANSOTOMY IN PARALYSIS AGITANS

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IN THE year 1952 we reported [1] that three procedures had been tried in attempts to influence beneficially the tremor of paralysis agitans: (1) interruption of afferent pathways in the midbrain tegmentum (mesencephalotomy), (2) reduction of the impulses passing from the thalamus to the striopallidum (thalamotomy), and (3) reduction of the pallidofugal impulses by lesions of the ansa lenticularis (ansotomy [1]). While unilateral interruption of the afferent impulses in the midbrain was unable to significantly diminish the tremor and thalamotomy had, at the most, only a slight effect for a few days, a definite reduction of the tremor could be obtained by ansotomy. In order to interrupt the pallidofugal fibers, Meyers [2] entered the third ventricle and incised its lateral wall. The author reports a favorable effect upon the tremor, but in view of his high mortality he considers the risks of this operation too great to warrant its general employment in the treatment of Parkinsonian tremor. Since we have had some experiences with stereoencephalotomy in operations on the basal ganglia in cases with choreic movements,[3] we applied a similar technique for interrupting the ansa lenticularis (ansotomy [1]) in tremor of paralysis agitans.

For a study of the changes in the state of innervation of the skeletal muscles of the extremities induced by ansotomy, a comparison of the tremorgrams and the electromyograms before and after operation seemed useful. The insertion of stereotactically guided needle electrodes presented the possibility of recording the electric activity of the globus pallidus simultaneously with the electrical discharges of the muscles of the shaking extremities.

## ANATOMICAL AND X-RAY STUDIES

For computation of the coordinates of the ansa lenticularis, the pineal gland or the posterior commissure initially was used if this gland was not calcified. However, we soon realized that a more exact localization, independent of the variations in the inclination of the brain in the skull, could be achieved if a reference point closer to the ansa lenticularis were available. For such a reference point the anterior commissure was chosen, since the globus pallidus in its anterior part rests upon the transversely coursing fibers of this commissure (Fig. 1). Its position in the midsagittal plane can be visualized by x-ray studies if one fills with air the anterior part of the third ventricle and its communication with the lateral ventricle through

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the foramen of Monro. For such studies lateral roentgenograms of the skull (Fig. 2) with the patient in the supine position on a tilting table and/or with dorsiflexion of the head so that the vertex is below the shoulders, as described by Twining,[4] proved very useful. However, one has to bear in mind that in this position the brain may be shifted somewhat posteriorly, and one has to correct such a shift by comparison with roentgenograms in the upright position.

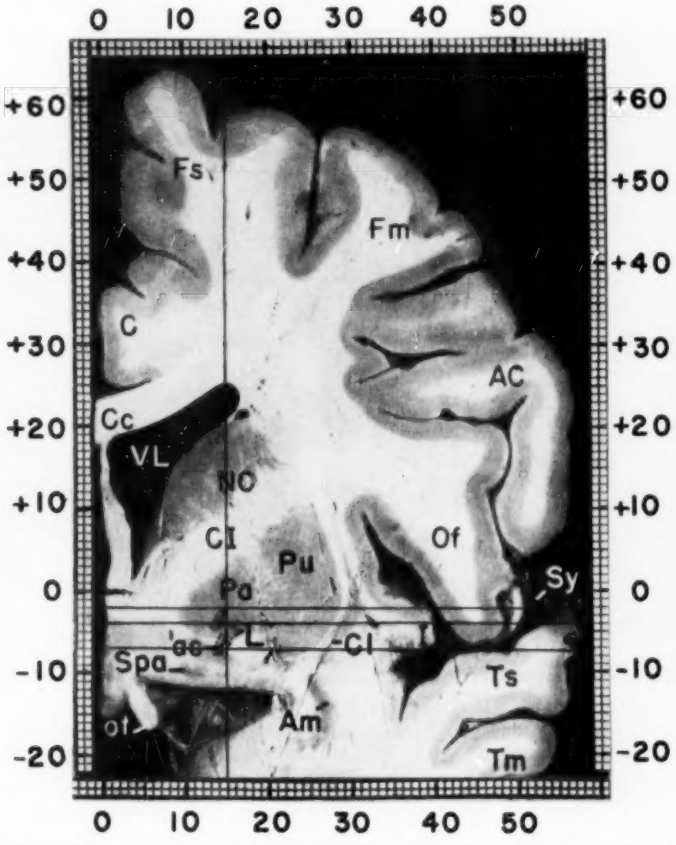


Fig. 1.—Frontal section through the transverse fibers of the anterior commissure (*ac*) showing schematically the location of the medially directed lesion (*L*) in and at the base of the pallidum (*Pa*) 15 mm. lateral to the midline. The wire of the electrode reaches from —2 to —4 and from —5 to —7. The horizontal line at —2 passes through the pole of the anterior commissure. The average extent of the electrolysis is indicated by the dotted line. The path of the electrode is not shown in this figure.

According to our measurements on anatomical specimens, the center of the anterior commissure lies in the median sagittal plane slightly anterior to, and 5-7 mm. ventral to, the center of the foramen of Monro. Furthermore, one has to bear in mind that the fibers of the anterior commissure, while coursing from the midsagittal plane lateralward, form a ventrally slightly concave arc (Fig. 1). In frontal

planes through this part of the anterior commissure, we found at 15 mm. lateral to the midline that the ventral border of the pallidum lies 2-4.5 mm. ventral to the pole of the anterior commissure, i. e., 2-4.5 mm. from the point where its central fibers intersect with the midsagittal plane. A line drawn in this frontal plane parallel to the median plane, 15 mm. laterally, passes through the medial part of the external division of the pallidum and reaches its base close to or slightly lateral to the ventral end of the internal medullary lamina. In more caudal levels the internal capsule is shifted lateralward, and the pallidum also is pushed more laterally the more caudal the sections one examines; e. g., the ventral end of the internal medul-

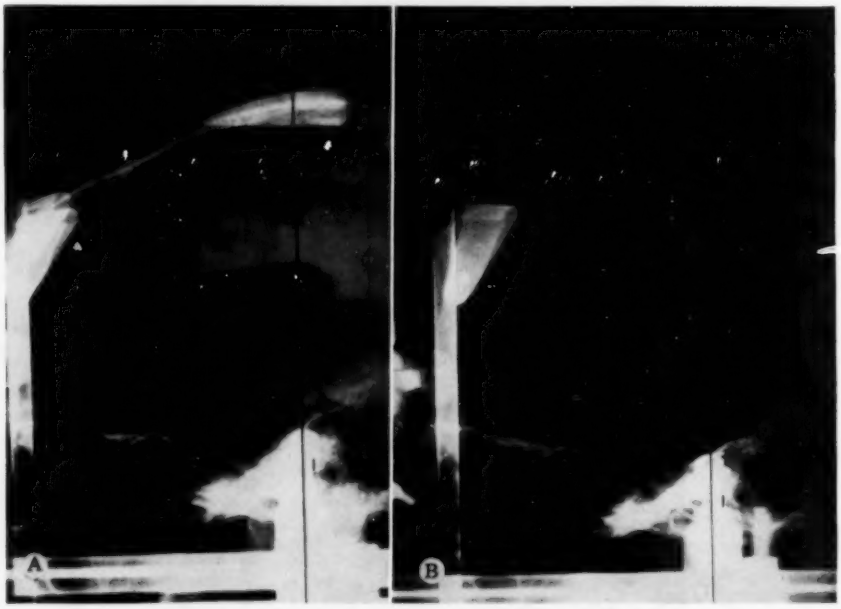


Fig. 2.—*A*, lateral roentgenogram with air-filling of the ventricles and visualization of the foramen of Monro; coordinates and direction of the punctures reaching the anterior commissure and a point 3 mm. behind it. *B*, postoperative x-ray study, showing location of a droplet of ethyl iodophenylundecylate (Pantopaque), injected corresponding to the posterior puncture (at *L*): *I* to *I*, interaural line.

lary lamina lies 13-15 mm. lateral at a level 25 mm. anterior to the posterior commissure; it is 15-18 mm. lateral at a level 20 mm. anterior to the posterior commissure (Table VI of our monograph [5]).

### INSERTION OF ELECTRODES FOR RECORDING OF PALLIDOGRAMS AND PRODUCTION OF LESIONS

On the basis of these anatomical findings, one puncture was performed in a sagittal plane 15 mm. lateral to the midline and the second 3 mm. behind, in a sagittal plane 17 mm. lateral. In order to avoid lesions of the internal capsule, the electrodes were inserted through the frontal lobe in a ventrocaudal direction, so

that their paths formed with the interaural plane an angle of 15-20 degrees (Fig. 2). The first puncture reached the base of the pallidum in a frontal plane through the transverse fibers of the anterior commissure; the second, 3 mm. posteriorly.

In order to record the electrical discharges of the ansa lenticularis and of the globus pallidus, concentric needle electrodes were used; and to produce lesions, our stylet electrode was employed.[5]

In view of the above-mentioned variability in the position of the ventral border of the pallidum in relation to the anterior commissure, the lesions were performed at two levels. At one level the tip of the wire electrode lay 2 mm. below the horizontal plane through the pole of the commissure; at the second level it was 5 mm. below that plane. The point of its exit from the electrode sheath was 2-4 mm. higher, depending on the length of protruding wire used, so that ventral parts of the pallidum were included in the lesion. In those cases in which the maximum lesions were produced, electrolytic anode lesions were made in medial and in posterolateral directions at both levels, using 10 ma. for one minute for each lesion. In those cases with the maximum lesions, a second puncture was performed 3 mm. further posterior at 17 mm. lateral, and again lesions in medial and posterolateral directions were produced at the levels indicated.

In calculating the depth of the lesion, one has to consider the curvature of the skull in the frontal plane, since one measures on the lateral views of the skull the distance of the anterior commissure from the cerebral surface in the median plane, while the actual puncture is made 15 and 17 mm. lateral to the midline. Therefore, one has to ascertain in anteroposterior views of the skull the distances of the cerebral surface from a horizontal (perpendicular to the median plane, e. g., through the supraorbital ridge) at 0 lateral and 15 mm. lateral. The difference of these measurements (average, 2 mm.) has to be deducted from the distance between the anterior commissure and the cerebral surface measured on lateral views of the skull in order to reach a horizontal plane through the pole of the anterior commissure by a puncture made 15 mm. lateral.

It seemed advisable to do the operation under local anesthesia. This enables one to observe the effect of each electrolytic lesion upon the tremor and also the ability of the patient to perform voluntary movements. In this way undesirable by-effects may be avoided as far as possible.

Up until the present time the method has been applied in six patients who had not been improved by routine medical treatment (two cases with idiopathic paralysis agitans and four with postencephalitic Parkinsonism).

## REPORT OF CASES

CASE 1.—Mrs. A. C., age 41, had influenza in 1918 and fractured the right forearm 14 years ago. Ten years prior to admission she noted a rhythmic tremor of the right upper extremity, which grew progressively worse. Two years prior to admission the right lower extremity and five months before her left side became similarly affected. On admission the right extremities were more involved than the left. The tremor in the right leg affected her walking in that she had to take shorter steps. The tremor would cease with voluntary movement, reappear when the extremities came to rest, and disappear with sleep, while excitement would intensify it. It was not alleviated by medication. There was a mild bilateral increase in tonus in all the limbs, without the cogwheel phenomenon.

Ansotomy on July 10, 1952. Under local anesthesia, with the pineal gland serving as reference point, electrolytic lesions were made in the region of the left ansa lenticularis. Immediately after operation there was practically no tremor in the right hand and leg except for a slight tremor of the right thumb, which was increased by emotion. Voluntary movements were not impaired, nor was the Hoffmann or Babinski sign present. There was likewise no disturbance of sensation or alteration in muscle tonus. She was discharged on the seventh postoperative day.

Nine months after operation her improvement still was maintained, and she reported that she was able to perform her home work with the right hand better than before the operation. Dynamometric readings: right hand, 12-16 kg.; left hand, 12-14 kg.

Eleven months after operation the right-sided tremor reappeared, so that it was thought advisable to add lesions of the ansa bilaterally, using a more precise localization by visualizing the foramen of Monro (June 18, 1953). Since this time the right side has been practically free of tremor, again without side-effects (duration of observation since the second operation, 5 months).

Case 2.—Mr. M. F., 47 years old, 27 years prior to admission had encephalitis and was in a coma for 48 hours. Shortly after this illness a tremor appeared in the left hand, then in the right hand, and somewhat in both legs. During the previous five years the tremor in both arms and legs had increased. This had been associated with weakness in both upper extremities, so that patient became unable to feed himself. For the previous five months the patient had been unable to walk. He had several oculogyric crises, which were somewhat relieved by amphetamine sulfate. He had taken practically every drug known that has been used in the treatment of the tremor of Parkinson's disease.

He presented a rather far-advanced stage of Parkinsonism. His speech was monotonous and very slow. At times his memory would wander. He had a mask-like facies and an oily seborrhea of the face and scalp. His vision was blurred because of the medication that he had been taking. He had a deformity of both hands, such as is typically seen in Parkinson's disease, and a bilateral foot drop. There was a constant, coarse tremor of the left arm and hand and frequent shaking of the right arm and hand. At times the tremor became so violent that the entire body would shake. Voluntary flexion and extension of the elbows, knees, and ankles showed very limited excursions. There was a questionable Hoffmann sign on the left side and a bilateral ankle clonus, which was almost inexhaustible.

On July 31, 1952, under local anesthesia, lesions were placed in the region of the right ansa lenticularis, with the pineal gland serving as reference point. After operation there was a reduction of the tremor in the left upper extremity. There did not appear to be any further impairment in volitional movements. On the fourth postoperative day he became somewhat lethargic and developed a temperature of 104 F.; this was most likely due to cystitis caused by an indwelling catheter. His urinary infection responded to treatment with sulfisoxazole (Gantrisin). About two weeks after operation he was fever-free. The tremor on the left side was still present but was less pronounced than before surgery.

Five weeks after operation his tremor on the left side had returned to about the same intensity as it was preoperatively. There was no evidence of pyramidal tract involvement following surgery except for the bilateral ankle clonus which was present preoperatively. There were no sensory disturbances.

Case 3.—Mr. N. W., age 43, in August, 1942, developed a high fever, lasting four to five days, which was associated with a period of unconsciousness, lasting three days. In 1946 a tremor appeared in both hands; it was first intermittent, but by 1948 it was noted constantly and involved both feet as well. It was more pronounced on the left side. There was also a stiffness of his muscles, which was partially alleviated by diligent exercises and medication. His condition grew progressively worse, and by 1950 he had already developed the typical propulsion gait with shortening of the steps. He tried many drugs including trihexylphenidyl (Artane), all of which failed to relieve him.

On examination he presented the typical Parkinsonian syndrome, with a fixed facial expression, oily seborrhea over the scalp and face, slow speech, bent-over attitude, propulsion gait with short steps, and a bilateral coarse rhythmic tremor involving both upper and lower extremities,

more pronounced on the left side, particularly in the left upper limb. Bilateral cogwheel rigidity was demonstrable, but this was not pronounced.

On Oct. 16, 1952, electrolytic lesions were placed in the region of the right ansa lenticularis. In this and in the subsequent cases the foramen of Monro served as a reference point. Ansotomy markedly reduced the tremor of the left hand without producing any paralysis. Associated with the reduction of tremor of the right upper limb there was decrease of rigidity to passive movements of the forearm and dorsiflexion of the wrist and diminution of the cogwheel phenomenon. Repeated closing and opening of the hand could be performed more quickly on the left side (10 times in 10 seconds) than on the right side (7 times in 10 seconds). He was discharged on Oct. 26, 1952, and readmitted on Jan. 11, 1953, for the same procedure on the left side. During this interval of time his improvement had not regressed, and there was a definite difference noted in the tremor and rigidity between the left and the right upper limb.

On Jan. 19, under local anesthesia, lesions were placed in the region of the left ansa lenticularis. The tremor was definitely reduced in the right hand and was without implicating volitional movements. Postoperatively he did not show any evidence of pyramidal tract involvement or of any sensory disturbances. The fixed facial expression, bent-over attitude, and tremors of the lower extremities did not appear to have been altered and his propulsion gait was still present.

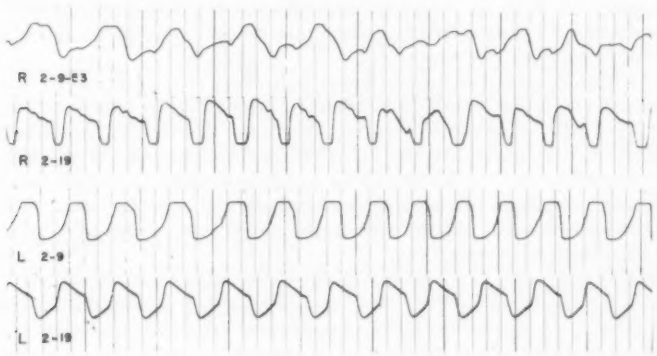


Fig. 3 (Patient G. R.).—Postencephalitic Parkinsonism. Photoelectric record of voluntary flexor-extensor movements of the fingers of the right (*R*) and left (*L*) hands before operation and one week after left-sided ansotomy. Recording time: 4.5 seconds.

His improvement had been maintained until he was last heard from (six months after the operation on the right side, three months after that on the left side).

Case 4.—Mr. G. R., aged 40, at the age of 16 had had what he described as "sleeping sickness." Three years prior to admission he noted a shaking of his right leg, occurring several times a day. Six months later the tremor spread to the right hand and forearm. It became progressively worse, so that he could neither feed himself nor use his hand for writing. It would subside on volitional movement and also during sleep. During the past six months he had been unable to work as a stevedore because of his tremor. He has taken scopolamine hydrobromide, without relief.

He presented a gross rhythmic tremor involving the upper and lower extremities on the right side. The tremor increased with tension or excitement, and at times it would become very violent, particularly in the upper extremity. There was no essential difference in the muscular tone between the right and the left upper limb. The tremor in the right lower extremity impaired his walking, so that his gait was slower than normal. The facies were mildly fixed.

On Feb. 12, 1953, electrolytic lesions were placed in the region of the left ansa lenticularis with the stereoencephalotome, under local anesthesia. Immediately following the electrolysis, there was noted an almost complete cessation of the tremor of the right upper and lower extremi-

ties. The frequency of alternating voluntary flexion and extension of the fingers (Fig. 3) was slower on the right side (19-22 per 10 seconds) than on the left side (28-32 per 10 seconds) before operation and became equal in the two hands after ansotomy (28-32 per 10 seconds). There did not appear to be any significant change in muscle tonus on either side. There were no signs of pyramidal tract involvement.

Ten Months After Operation: Patient works in a rubber factory. There is no tremor visible at rest or on exertion. He reports that a tremor, and then slight, appears only if he is hungry. The dynamometric readings, which were, 12 days after the operation, right hand 20-22 kg., left hand 22-24 kg., are, at present, right hand 38-42 kg., left hand 32-38 kg.

Case 5.—Mr. S. P., 29 years old. At the age of 2 years he had a laceration of the left wrist, when his hand was caught in a clothes wringer. There was no past history of encephalitis or influenza. In 1949 he noticed a sudden onset of shaking of his left wrist. Gradually this became worse, particularly in the hand and wrist, and spread to involve his left lower extremity.

On examination he presented a facial expression of immobility, slow speech, and a unilateral coarse tremor on the left side, more pronounced in the upper than in the lower limb. It would come to rest with volitional movements. There was a mild cogwheel phenomenon demonstrable in the left upper extremity. The gait was slow.

On July 17, 1950, under local anesthesia, bilateral electrolytic lesions were placed in the region of the dorsomedial nuclei of the thalamus. Following operation there was a transitory reduction of the tremor in the left upper extremity; however, on the date of discharge, July 27, it was felt that there was no essential improvement.

On Feb. 7, 1952, additional electrolytic lesions were placed in the midbrain tegmentum at the level of the posterior commissure on the right side, interrupting the sensory pathways. It was hoped that a reduction of peripheral stimuli to the higher centers might beneficially influence his tremor. After this operation, there was a definite hypalgesia on the left side, involving particularly the left arm and the left side of the face. The sensation of touch and deep sensation were preserved. There were no gross motor disturbances. The tremor was still present but appeared somewhat reduced. However, when the patient was discharged, his tremor was essentially the same as before operation.

On March 19, 1953, under local anesthesia, electrolytic lesions were placed in the region of the right ansa lenticularis. Immediately after the ansotomy there was noted a definite reduction of the tremor with preservation of volitional movements. The remaining tremor appeared to affect mostly the middle finger of the left hand. Postoperatively there was no sign of pyramidal tract impairment, no disturbance in the speed of flexor-extensor movements (preoperatively: left 23-28 per 10 seconds, right 25-32 per 10 seconds; one week after operation: left 23-35 per 10 seconds, right 20-33 per 10 seconds), only a slight diminution of motor power (preoperatively: left hand 10-16 kg., right hand 21-26 kg.; one week after operation: left hand 8-12 kg., right hand 16-22 kg.), and no change in the sensory findings. Approximately one week following discharge from the hospital the tremor recurred, but not with its former severity.

On reexamination on Dec. 1, 1953 (eight and one-half months after operation), the patient reported that the tremor had continued to decrease. For many days his hand does not shake at all, and the tremor appears only on excitement. At present patient takes no medication. He is working in a dress factory and is able even to thread needles. The dynamometric readings on the left side have improved (left hand 14-18 kg.; right hand 22 kg.). The speed of flexor-extensor movements of the fingers is nearly equal on the two sides (left 30-35 per 10 seconds; right 32-35 per 10 seconds). On examination he showed only a slight tremor, which was increased by voluntary efforts. There is no tremor in his leg, and his walking is much improved as compared with his preoperative gait.

Case 6.—E. K., male, age 40. In 1945 he began to stutter; in 1947 there developed an involuntary shaking of his right arm and hand. This became progressively worse, so that by 1952 he had to discontinue working. At the United States Naval Hospital in Philadelphia a diagnosis of Parkinson's disease was made. He gave a history of some type of "fever" while in the armed services in 1944. At the Naval Hospital he was given some medication, which gave him little relief.

On examination on May 11, 1953, the facial expression appeared flattened. There was slowing of the movements, particularly of the right hand (alternating flexor-extensor movements of the fingers on the right side 10-16 per 10 seconds, on the left side 21-29 per 10 seconds), and a propulsion type of gait, a marked rhythmic tremor of the right hand and forearm, and a mild tremor of the right lower extremity. Dynamometric readings: right hand 24-32 kg.; left hand 22-28 kg.

On May 21 lesions were made in the region of the left ansa lenticularis, under local anesthesia. Postoperatively there was almost a complete elimination of the tremor of the hand without any associated paralysis.

On discharge, May 30, there was noted but a slight tremor of the hand. Alternating flexion and extension of the fingers were recorded as 28-34 per 10 seconds on the right side and 27 per 10 seconds on the left side. Dynamometric readings: both hands, 28 kg. Hoffmann and Babinski signs were not elicited.

On reexamination (July 21 and Dec. 15, 1953) the amplitude of the tremor was still definitely reduced as compared with that before operation. It increases when patient is tired in the evening. He is able to eat soup with a spoon, while before operation he spilled it.

*Summary of Cases.*—Ansotomy influenced the Parkinsonian tremor beneficially in the opposite extremities in that it ceased almost completely (Cases 1 and 4) or became definitely diminished in amplitude. In Case 3 at least some diminution of the amplitude and frequency of the tremor of the hands was observed, while the tremors of the lower extremities, fixed facial expression, bent-over attitude, and propulsive gait were not altered. In Case 2 the tremor was affected for only a short period (about four weeks). In Case 1 reappearance of the tremor after 11 months necessitated an enlargement of the lesion in the ansa lentiformis, which, again, resulted in nearly complete elimination of the tremor on the opposite side. The long-range effects, beyond observation periods of several months, in the other cases remain to be studied.

In contradistinction to the paralyzing effect of operations in the cortex or spinal cord, no pyramidal tract signs, such as the Hoffmann or Babinski, or increase of the tendon reflexes on the affected side was present, and the voluntary movements were preserved in all cases. Contrary to expectations, ansotomy failed to increase the muscle tone. In Case 3 there was even some reduction of the resistance to passive movements of the forearm and to dorsiflexion of the wrist and diminution of the cogwheel phenomenon. The ability to perform alternating movements in quick succession was not impaired, and in Cases 3, 4, 5, and 6 it was even improved (Fig. 3). In Case 3 this was associated with a reduction of the muscle tone; in Cases 4, 5, and 6 the increase in frequency of alternating movements occurred without definite changes of muscle tone. There was no impairment of sensation.

It may be of interest to compare our results with the effects of procedures also acting on the region of the globus pallidus and reported subsequent to our preliminary note on ansotomy. Cooper [6] found that ligation of the anterior choroidal artery is able to relieve resting tremor and cogwheel rigidity. Since this blood vessel supplies not only the globus pallidus and the ansa lenticularis but also the red nucleus, the corpus Luysi, the substantia nigra, the retrolenticular portion of the internal capsule, the cerebral peduncle, and the optic tract, it is difficult to relate the effect of this operation to a specific structure. The variability in the extent of the area supplied by the anterior choroidal artery and the possibility of side-effects due to impairment of circulation in the optic tract and in the cerebral peduncle should also be borne in mind.

Narabayashi and Okuma [7] injected a procaine-oil mixture into the globus pallidus by means of the stereotactic technique for treatment of rigidity and tremor in Parkinsonism. According to the authors, these disturbances were abolished in

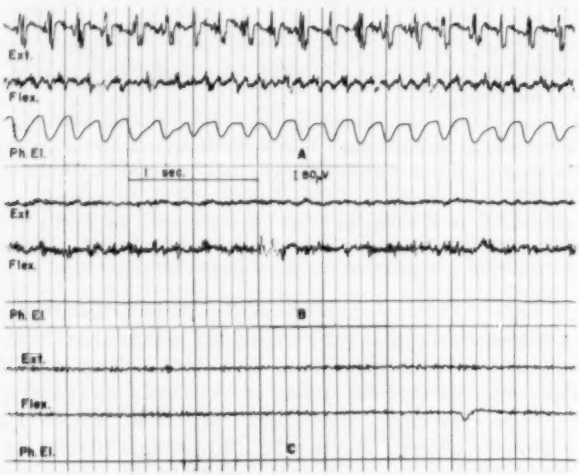


Fig. 4 (Patient G. R.).—Postencephalitic Parkinsonism. Electromyograms of the extensors (*Ext.*) and flexors (*Flex.*) of the right forearm and photoelectric tremorgrams of the right fingers. *A*, before ansotomy; *B*, 2 weeks after, and *C*, 10 months after, left-sided ansotomy.

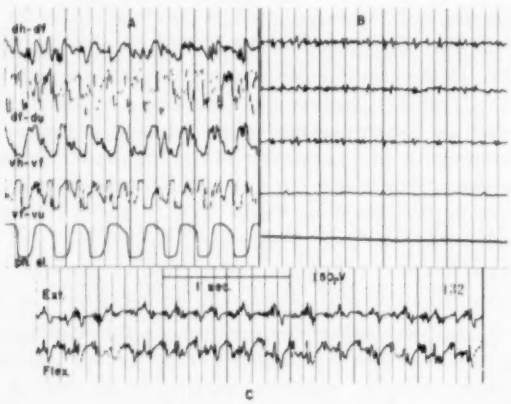


Fig. 5 (Patient S. P.).—Idiopathic paralysis agitans. Electromyograms of the left forearm and photoelectric tremorgrams of the left fingers. Abbreviations are as follows: *dh* (*vh*), dorsal (ventral) aspect of hand; *df* (*vf*), dorsal (ventral) aspect of forearm; *du* (*vu*), dorsal (ventral) aspect of upper arm; *Ext.*, extensors of forearm; *Flex.*, flexors of forearm; *A* and *C*, before operation; *B*, one week after right-sided ansotomy.

two to three minutes after operation; they tended to reappear in two to three months but were less severe than before the operation. A permanent effect of such an injection, of course, could not be expected.

### EFFECT UPON THE TREMOR AS REFLECTED IN TREMORGRAMS AND ELECTROMYOGRAMS

In order to record and to analyze the effect of ansotomy upon the tremor, motion pictures,* tremorgrams, and electromyograms were taken. Figures 4 and 5 show tremorgrams recorded by placing a finger or the hand of the patient between a flashlight and a photoelectric cell, which was connected with a channel of the Grass electroencephalograph, care being taken that the distances between the flashlight, the photoelectric cell, and the shaking part, as well as the position of the latter, the intensity of the flashlight, and the sensitivity of the electroencephalograph, remained identical on repeated tests. These tremorgrams demonstrate that ansotomy may be able definitely to diminish the tremor amplitude and sometimes even to abolish the tremor completely in the extremities opposite the operation.

Electromyograms of the flexors and extensors of the arm show preoperatively typical rhythmical bursts of spikes that alternate in the antagonistic muscles (Figs. 4 and 5). However, it should be pointed out that such an alternation of the electrical discharges was not invariably found. In one of our patients (Case 5) who had a typical Parkinsonian tremor, prolonged recording revealed also simultaneous appearance of the bursts in the flexor and extensor muscles (Fig. 5C). Similar observations were reported by Jung.[8]

Ansotomy induced various changes (Figs. 4 and 5). Electrical signs of muscular activity were hardly demonstrable in positions in which preoperatively definite groups of spikes appeared, or there was only a continuous sequence of discharges of small amplitude, or the amplitude of the rhythmical bursts of spikes was definitely reduced. In Case 3 a reduction of the frequency (from 4.3 to 4.0 per second) was noticed. Sometimes rhythmical bursts were still present, although a tremor neither was visible on inspection nor could be recorded by the above-described method (Fig. 5*B*). Of particular interest is the disappearance or reduction of the rhythmical discharges in some muscle groups, e. g., the extensors of the forearm while such discharges still appeared in discrete groups in the antagonists.

### ELECTRICAL ACTIVITY OF THE GLOBUS PALLIDUS

Electrograms of the pallidum and of the ansa lenticularis were recorded simultaneously with scalp EEG's and with the electromyograms of the flexors and extensors of the opposite arm (Figs. 6 and 7). Since local anesthesia was used, the tremor persisted, and typical rhythmical bursts of the affected muscle groups could be recorded. Distinct, regular rhythmical electrical discharges could be recorded from the globus pallidus at frequencies varying between 11 and 16 per second. There were, however, no fluctuations of the discharges corresponding with the tremor rhythm in the EEG or in the pallidogram.

### COMMENT

In view of the small number of observations and the lack of histological controls, definite conclusions particularly regarding the long-range effects and the role of the

* Presented at the Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 15, 1953.

pallidum in the mechanism of tonus innervation and in the genesis of the tremor must be postponed; only a few preliminary remarks on the pathophysiology of the tremor and the influence of ansotomy may be offered.

Previous investigators have found that in cases of paralysis agitans neither the electric activity of the cortex, as revealed in the scalp EEG (Jasper and Andrews [9]; Schwab and Cobb [10]; Jung [8]; Ward and associates [11]), nor that of the corpus striatum and "neighboring structures" † (Meyers, Hayne, and Knott [12]) reveals a relation of their frequencies to that of the tremor. We were able to make similar observations not only regarding the EEG but also for the electrogram of the pallidum and its efferent fibers (Figs. 6 and 7). Thus, the area of origin of the tremor rhythm is to be sought below the globus pallidus.

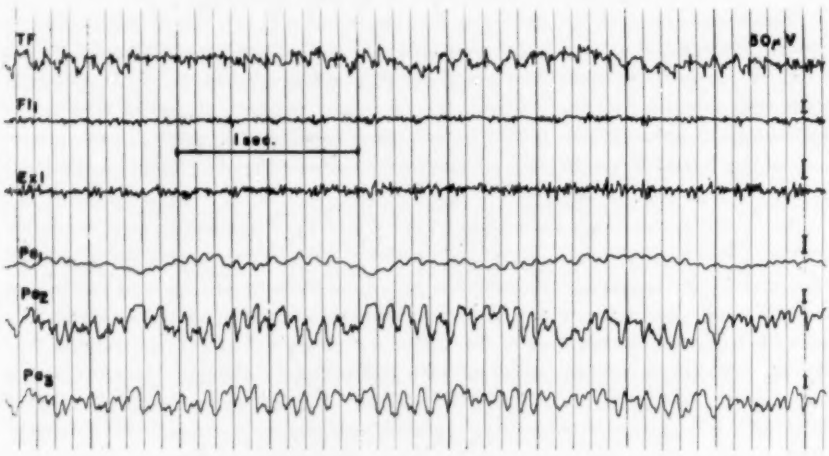


Fig. 6 (Patient N. W.).—Postencephalitic Parkinsonism. Electropallidograms ($Pa_1$ from the ventral surface of the right globus pallidus, $Pa_2$ and $Pa_3$ from the interior of the right pallidum); bipolar electrodes. *Fl l*, electromyograms of the flexors of the left forearm; *Ex l*, electromyograms of the extensors of the left forearm; *TF*, scalp EEG (temporofrontal leads on the right side). Local anesthesia plus meperidine (Demerol) hydrochloride U.S.P., 150 mg.; pentobarbital (Nembutal) sodium, 100 mg.; atropine sulfate, 0.4 mg.

† In order to ascertain the position of the electrode that had been introduced by hand, Meyers and associates carried out pneumoencephalography while the electrode shaft was *in situ*. They compared the position of the electrode shaft as revealed in the lateral pneumoencephalogram with a photograph of the medial aspect of a formalin-hardened brain, in which chords were placed "approximately perpendicular to the anteroposterior axis of the hemisphere." Postmortem deformation and volume changes of the brain after it had been removed from the skull, as well as individual variations, were not taken into consideration. The angle between the direction of the electrode and the chords was not and could not be determined accurately. In view of the length of the inserted electrode, small differences in the direction of the electrode and that of the chords may have caused a considerable error at the depth reached by the electrode. It seems, therefore, hardly possible to state with certainty that the authors were able to place the electrode in a relatively small ganglion such as the globus pallidus. In one autopsied case they found a punctured canal on a horizontal section close to the external surface of the pallidum. However, it seems uncertain whether the electrode remained in this structure at deeper levels.

The frequencies observed in the globus pallidus were not significantly different from those observed in the cerebral cortex and in the thalamus in patients without organic changes in these areas; consequently gross pathologic changes in the globus pallidus are rather improbable. This seems to indicate that severe impairment of this ganglion is hardly a prerequisite for the development of the tremor. The occasional occurrence of Parkinsonism after extensive pallidal lesions (Alexander [13]) may be due to the development of secondary changes in the substantia nigra, since experimental lesions of the striopallidum induce degenerative changes in cells of the substantia nigra (von Monakow [14]; Ferraro [15]; Dresel and Rothmann [16]).

Several observations point to the possible role of the reticulate substance of the rhombencephalon and/or mesencephalon in the genesis of static tremor. The importance of reflexes synapsing in the reticulate substance for the normal static innervations has long been recognized (Bernis and Spiegel,[17] 1925; Bach and Magoun,[18] 1947), and the static tremor may be regarded as a pathologic aberration of this mechanism. In fact, prolonged stimulation of points of the tegmentum may first

Fig. 7 (Patient S. P.).—Idiopathic paralysis agitans. Electropallidograms recorded from the ventral surface ($Pr_1$) and the interior of the right globus pallidus ($Pr_2$, $Pr_3$). *RFO* indicates EEG from right-sided fronto-occipital scalp; *LE*, *LF*, electromyograms of the extensors and flexors of the left forearm. Local anesthesia plus morphine hydrochloride, 50 mg.; atropine sulfate, 0.4 mg.; pentobarbital, 150 mg.

induce tonic reactions and eventually result in tremor (Folkerts and Spiegel [19]). After the observation that stimulation of the mesencephalic and pontine tegmentum may induce tremor in cats (Spiegel, Kletzkin, and Szekely [20]; Folkerts and Spiegel [19]), similar experiences were reported in monkeys (Jenkner and Ward [21]).

When comparing the effect of threshold stimulation of tremorgenetic points of the tegmentum in the caudal parts of the midbrain or in the pons before and after lesions were produced in the cranial part of the midbrain, Folkerts and Spiegel [19] found that lesions of the substantia nigra are able to increase the amplitude of the tremor obtained on tegmental stimulation. This seems to suggest that the substantia nigra sends inhibitory impulses to the reticulate substance and may explain the appearance of the tremor following lesions of the ventral part of the tegmentum (Ward and associates [11]; Peterson and associates [22]) as due to release from nigral inhibition. The substantia nigra, however, is not the only region sending inhibitory

impulses to the reticulate substance, since Folkerts and Spiegel observed an increase in the tremor amplitude on tegmental stimulation also after lesions in the area of the nucleus ruber.

It seems tempting to apply these observations in animal experiments to the human pathology, particularly in view of the fact that in Parkinsonian tremor the severest degeneration is found in the substantia nigra (e. g., Davison [23]). The long duration of the tremor, often for years, suggests that one deals with a release phenomenon. It may, therefore, perhaps be suggested as a working hypothesis that the Parkinsonian tremor is due to release of the reticulate substance of the midbrain

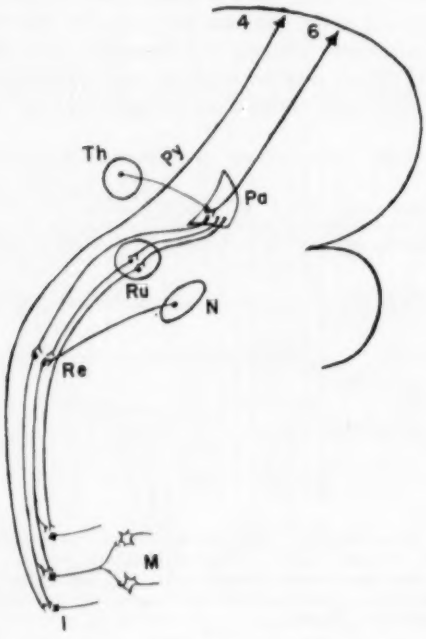


Fig. 8.—Schematic diagram of a possible mechanism of static tremor. The tremor originates in the reticulate substance (*Re*) of the midbrain and rhombencephalon which sends impulses to the spinal cord. *I* is internuncial cell; *M*, anterior horn cell. Facilitating impulses originate in Area 6 and in the pallidum (*Pa*), and inhibitory impulses in the substantia nigra (*N*) and the nucleus ruber (*Ru*). Thalamic impulses (*Th*) may excite the pallidum. The pyramidal tract (*Py*) probably carries facilitating and inhibitory impulses.

and rhombencephalon from inhibiting impulses originating chiefly, but not exclusively, in the substantia nigra (Fig. 8).

If we consider the reticulate substance of the midbrain and pons as a tremorgenetic area, such a statement needs a qualification. The fact that stimulation of the reticulate substance of the tegmentum or lesions releasing it from inhibitory impulses may induce tremor suggests that at least one component of the tremor, the innervation of rhythmical bursts of impulses, may originate in this area. It is, however, possible that the mechanism of another important, although not absolutely constant

(Fig. 5C), characteristic of the static tremor, the alternation of activity in antagonistic muscles, is localized in spinal levels, since it is well known that spinal circuits are sufficient for the reciprocal innervation of antagonists.

The experience that lesions of the ansa lenticularis are able to diminish, or even to abolish, the tremor suggests that at least a part of the pallidofugal impulses has a facilitating effect upon the tremor-genetic area of the reticulate substance.

Ansotomy interrupts, of course, only that part of the pallidofugal fibers that emerge at the ventral border of this ganglion, while most of the fibers leaving it on its dorsomedial border remain intact. That these two groups of fibers have different connections and, consequently, probably also different functions is suggested by Ranson's [24] studies of Marchi degenerations following experimental pallidal lesions. It should also be borne in mind that the pallidum may be a part of a facilitating, as well as an inhibitory, circuit, as found by Hodes and associates [25] and Peacock and Hodes [26] for the knee jerk and cortically evoked foreleg flexion.

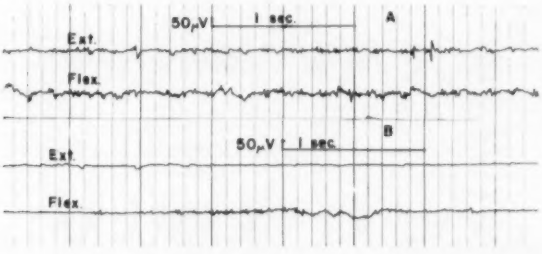


Fig. 9 (Patient G. R.).—Postencephalitic Parkinsonism, three months after left-sided ansotomy. Electromyogram of the extensors (*Ext.*) and flexors (*Flex.*) of the right forearm. *A*, blood sugar 99 mg. per 100 cc.; *B*, 173 mg. per 100 cc.

To what extent the elimination of facilitating impulses may be able to reduce the tremor may depend on various factors, e. g., the degree of overactivity or release of the tremor-genetic cell groups of the reticulate substance, the amount of activating impulses from afferent nerves and from other centers, and the role of possible metabolic or toxic stimuli.

In this respect an observation in Case 4 may be of interest. In this patient some degree of tremor appeared when he was hungry and his blood sugar level was low, while following ingestion of dextrose and subsequent increase of his blood sugar a tremor was hardly visible (Fig. 9). This observation could not be repeated in our other cases.

The origin of the facilitating impulses transmitted by the ansa lenticularis can only be surmised at present. The observations that elimination of cortical Areas 4 and 6a (Bucy and Case [27]) or of Area 6a alone (Putnam [28]) may reduce or abolish the tremor may perhaps suggest that facilitating impulses to the reticulate substance originate in Area 6 and synapse in the pallidum. This concept, however, is offered as a working hypothesis only.

A few remarks regarding the relationship of the pyramidal tract to the genesis of the Parkinsonian tremor may be added. Hoefer and Putnam [29] wisely point out

that the function of the pyramidal tract is ambivalent in this respect. While in most cases volitional impulses inhibit the Parkinsonian tremor, one can occasionally observe that such impulses are able to increase the tremor, as was also evident in our material. This may be due partly to facilitating impulses in the pyramidal tract, partly to fatigue; when patients repeatedly performed a task, such as closing and opening the hand, and became fatigued, we could observe that the initially tetanic contractions broke up into interrupted bursts of impulses (Fig. 10). In instances in which facilitating impulses in the pyramidal tract are demonstrable, it would be comprehensible that elimination of pyramidal impulses would be able to abolish the tremor. However, for the apparently larger group of cases in which voluntary efforts suppress the tremor, the view that the pyramidal tract carries tremor impulses is hardly applicable. The absence of the tremor rhythm in the EEG is also difficult to reconcile with the pyramidal tract theory. Putnam [28] found, on the one hand, that section of the anterolateral tract of the spinal cord does not affect the tremor, while extensive lesions of the lateral column, including the area of the pyramidal tract,

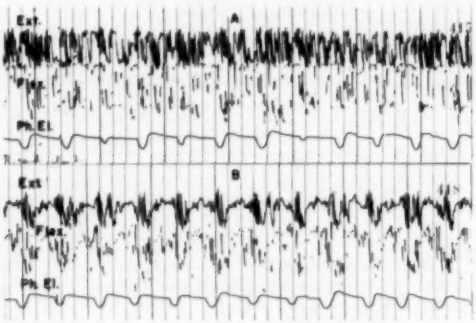


Fig. 10 (Patient G. R.).—Postencephalitic Parkinsonism, two weeks after left-sided ansotomy. Voluntary flexion-extension of the fingers of the right hand. *Ext.* and *Flex.* indicate electromyograms of the extensors and flexors, respectively, of the right forearm; *Ph.El.* is a photoelectric record. The patient squeezes a rubber balloon connected to a tambour. The movements of its lever throw a shadow on the photoelectric cell. Note that the electric discharges in the extensors are first continuous (*A*), then become discontinuous (*B*).

are able to eliminate or to reduce it. These observations may perhaps be interpreted without assuming that the pyramidal tract carries the impulses innervating the tremor if one remembers that the centrifugal fibers from the reticulate substance course in the spinal cord in the reticulate formation of the white matter closely adjacent to or overlapping the medial part of the lateral corticospinal tract, so that reticulospinal fibers are easily interrupted by Putnam's operation. Oliver's [30] experience that complete section of the lateral column results in greater reduction of the tremor than pyramidotomy seems to support such an interpretation. The disappearance of the tremor following lesions of the internal capsule (for instance, one of Parkinson's ‡ original cases; however, for contrary experiences, see Mettler and associates [33] and Davison [23]) may also be due to a lesion of overlapping or adjacent extrapyramidal or parapyramidal fibers.

‡ References 31 and 32.

## SUMMARY AND CONCLUSIONS

A stereotaxic method for localizing and producing lesions of the ansa lenticularis (ansotomy) has been developed using the foramen of Monro and the anterior commissure as reference points.

Ansotomy is able to reduce and, in some instances, almost completely to eliminate the Parkinsonian tremor on the opposite side. These results could be obtained with preservation of volitional movements or without increase of muscle tone or disturbance of sensation. The ability to perform alternate movements, e. g., flexor-extensor movements of the fingers, may even be increased and rigidity sometimes diminished.

The electropallidogram failed to show a relationship of its rhythm to that of the tremor or abnormalities indicative of gross pathologic changes.

Based upon these experiences and upon animal experiments (combination of tegmental stimulation and mesencephalic lesions), a working hypothesis regarding the mechanism of the Parkinsonian tremor is outlined. It is assumed that the static tremor is due to a release of the reflex arcs serving static innervation and synapsing in the rhombencephalic and mesencephalic reticulate substance from inhibitory influences that originate chiefly, but not exclusively, in the substantia nigra.

The part of pallidofugal impulses conducted by the ansa lenticularis probably carries facilitating impulses to the tremor-genetic area in the tegmentum. The role of other pallidofugal fibers is being studied.

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# EFFECT OF PINEAL EXTRACTS ON BLOOD GLUTATHIONE LEVEL IN PSYCHOTIC PATIENTS

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THE FUNCTION of the pineal gland is not established; evidence bearing on this matter has been reviewed in another publication from this laboratory.[1] The possibility that the pineal gland might influence metabolism in man has not been investigated extensively in the past, and it was therefore decided to make such a study here. Some negative findings were encountered; a constant positive finding was that the blood glutathione level changed during a course of injections of some pineal extracts. This was considered important since earlier work [2] had shown that the blood glutathione level is low in many patients with manic-depressive, involutional, or schizophrenic psychoses. A few observations on glucose tolerance were also made, in view of the belief currently held by some workers that glutathione influences carbohydrate metabolism.

## MATERIAL AND METHODS

Nine experiments were performed with four pineal extracts, designated in this laboratory as A, RPA-4, TRPA-4, and TSD-D; 40 experiments using 10 other types of extracts will not be discussed here, since their administration caused less significant changes or no change at all. Details of the preparation of these extracts will be presented in another paper. The patients given these extracts had manic-depressive (Cases F, G, H, I), involutional (Case E), or schizophrenic (Cases A, B, C, D) psychoses. They ranged in age from 25 to 68 years; three were women.

The patients were given intramuscular injections every day or every other day; the volume injected was between 2.5 and 10 cc. each time. No fever, change in pulse rate or blood pressure, rise in blood leucocyte count or sedimentation rate, or fall in blood eosinophile count occurred during the course of the injections here reported.

The methods of study used were those previously described for blood glutathione,[2] blood sugar,[3] and urinary 17-ketosteroids.[4] Measurements of blood glutathione level were made two or three times a week; the number of measurements made in each patient ranged from 2 to 25 in the control period and from 4 to 13 during the administration of the extracts.

Aided by a grant from The Wilson Laboratories, Chicago.

From the Laboratory of Clinical Physiology, McLean Hospital, Waverley, Mass., and the Department of Medicine, Harvard Medical School.

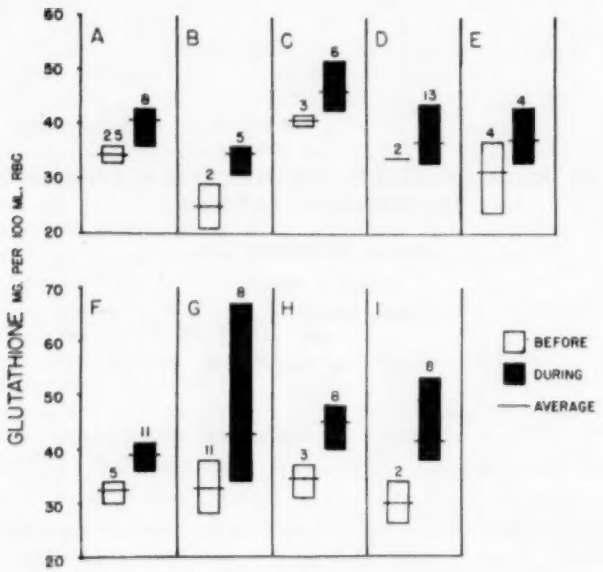


Chart 1.—Blood glutathione level before, and during, administration of pineal extracts. The numbers over each rectangle indicate the number of separate determinations made in the periods indicated.

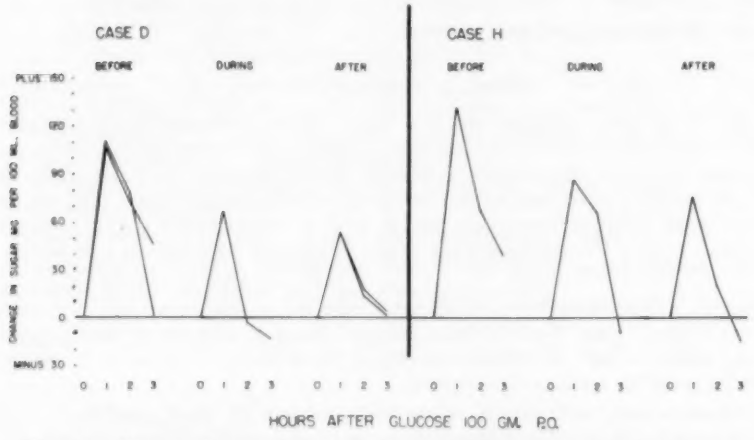


Chart 2.—Glucose tolerance before, during, and after period of administration of pineal extracts. Two tests were done before, and again after, this period in Case D.

OBSERVATIONS

Before the extracts were administered, the average blood glutathione levels ranged between 25.0 and 41.0 mg. per 100 ml. of erythrocytes; the mean value was 32.7 mg., with a standard deviation of 4.1 mg. (Chart 1). During the period of administration of the extracts, the average blood glutathione levels ranged between 34.6 and 46.3 mg. per 100 ml.; the mean value was 40.5 mg., with a standard deviation of 3.6 mg. (Chart 1). The range of values found in individual cases before and during the course of injections showed no overlapping in six of the nine experiments and a small degree of overlapping in three. In all nine experiments, however, the individual averages during the administration period were higher than in the control period. The difference ranged between 3.0 and 11.4 mg. per 100 ml. of erythrocytes; the average difference was 7.5 mg., or 23% of the over-all control average (Chart 1).

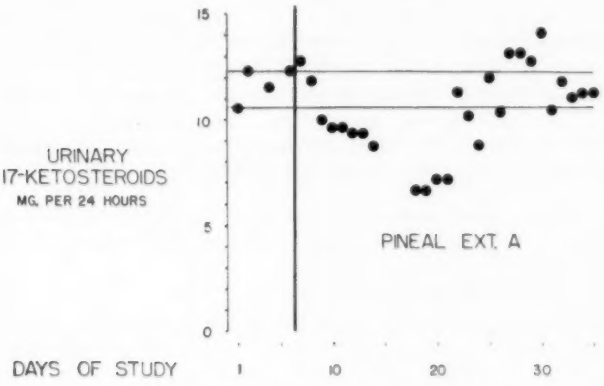


Chart 3.—Effect of a pineal extract on 17-ketosteroid output.

One of the three patients had normal glucose tolerance in the control period; this did not change during the administration of pineal extract. The two other patients, in whom the control glucose tolerance curves were abnormal, showed lowering of the curves in the administration period (Chart 2).

COMMENT

Administration of the pineal extracts used in the present study caused a significant rise in blood glutathione level in psychotic patients. This rise was accompanied by improvement in glucose tolerance in the two patients whose control curves were abnormal.

The mechanism of the effect of these extracts on blood glutathione concentration is unknown. The mechanism by which impaired glucose tolerance was restored to or toward normal also is obscure. All the patients in the present study (and also those who received other extracts) showed rises in blood eosinophile counts ranging between 60 and 200% during the period of extract administration. In order to test the hypothesis that improvement in glucose tolerance was due to depression of adrenal cortex function, measurements of urinary ketosteroid excretion were

made in one patient (Case D). A significant decrease occurred, but it did not persist beyond the 14th day of extract administration (Chart 3); on the other hand, the glucose tolerance continued to improve beyond that time. Apparently more than one factor is involved in the improvement in glucose tolerance observed here.

## SUMMARY AND CONCLUSIONS

The administration of certain pineal extracts caused increases in blood glutathione level in nine patients with manic-depressive involutional, or schizophrenic psychoses. Glucose metabolism was simultaneously restored to or toward normal in two patients with abnormal control glucose tolerance curves. Evidence of depression of adrenocortical function was observed in the one patient whose 17-ketosteroid output was studied.

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# EFFECT ON ELECTRICALLY INDUCED CONVULSIONS OF THE NUMBER OF PREVIOUS TREATMENTS IN A SERIES

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ANYONE who gives electric shock treatments is bound to have observed that the convulsion threshold rises successively during a series of treatments and then seems gradually to become stable. Some weeks after the final treatment the convulsion threshold is found to have resumed its original level. Kalinowsky [1] refers to this phenomenon, which had been observed by Elsberg and Stookey [2] before the introduction of electric shock therapy. Bárány and Stein-Jensen [3] found the same tendency in animals. Toman and Goodman,[4] in their experiments with animals, carefully studied the inhibitory period during some hours immediately after the electroconvulsions.

As I had observed that the duration and intensity of the convulsive seizure appeared to decrease, while the convulsive threshold was increased during series of shock treatments, I thought it worth while to study these effects more closely.

## METHOD AND MATERIAL

First, the duration of the convulsions was calculated for a material consisting of 1,666 routine electric shock treatments. In these cases a few breaths of pure oxygen were given before the shock.

Second, the duration of the convulsions was estimated for a material of 510 electric shock treatments administered in connection with a muscle relaxant (succinylcholine iodide, 0.3 mg. per kilogram of body weight, together with hexobarbital sodium [Evipan sodium] 0.15-0.20 gm. intravenously, and oxygen inhaled one minute prior to the shock) according to Holmberg and Thesleff.[5]

Third, the duration and intensity of the convulsions and the frequency of the clonic jerks were studied by means of a special electromyographic method (Holmberg [6]). This material consisted of 39 cases, in which quite unmodified treatments were given.

In all these cases the shock treatments were administered twice a week, but as an exception the interval between two treatments could be a week.

## RESULTS

A. *Calculations for 1,666 Routine Treatments.*—In all the electric shock treatments the duration of the convulsive seizure was measured with a stop watch. This method was imperfect, since the figures tended somewhat to cluster around the numbers of seconds ending in zero and five. It was clearly demonstrated, however, that the duration of the convulsions decreased considerably during the series of treatments; this was most evident at the beginning of the series (Chart 1 and Table 1).

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As will be seen from the tables, the difference in duration was not great, but between Shock 1 and Shock 2 it was highly significant. Between Shocks 2 and 3 and between Shocks 3 and 4 it was nearly significant. For the remainder of the series there was no significant difference.

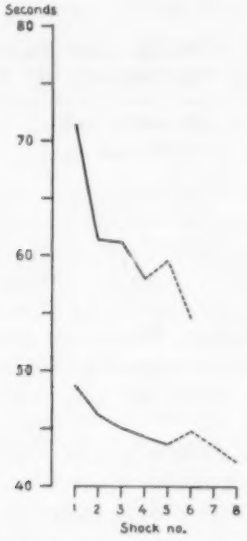


Chart 1.—Duration of convulsions during series of electric shock treatments, with administration of only a small amount of oxygen (lower curve) and with a muscle-relaxing drug and oxygenation (upper curve).

TABLE 1.—*Duration of Convulsions (in Seconds) in a Series of Routine Electric Shock Treatments, Preceded by Only a Few Breaths of Oxygen*

| Shock No. | Duration of Convulsions | No. of Cases | Difference | *df* | *t* | *P* |
|---|---|---|---|---|---|---|
| 1 | 48.7 ± 0.52 | 329 | | | | |
| | | | 2.49 ± 0.483 | 321 | 5.146 | < 0.001 |
| 2 | 46.2 ± 0.46 | 348 | | | | |
| | | | 0.98 ± 0.401 | 341 | 2.437 | < 0.05 |
| 3 | 45.1 ± 0.40 | 350 | | | | |
| | | | 0.94 ± 0.436 | 273 | 2.151 | < 0.05 |
| 4 | 44.3 ± 0.44 | 280 | | | | |
| | | | 0.37 ± 0.594 | 186 | 0.626 | |
| 5 | 43.7 | 188 | | | | |
| 6 | 44.8 | 102 | | | | |
| 7 | 43.5 | 51 | | | | |
| 8 | 42.1 | 18 | | | | |

B. *Calculations for 510 Treatments in Connection with Muscular Relaxation.*—The duration of the convulsions was measured with a stop watch also for this material. The method was somewhat inexact, as the faint jerks toward the end of the seizure were at times difficult to observe. As a result of the technique applied, which insures normal oxygen saturation during the entire seizure (Holmberg [7]), the convulsions were prolonged very considerably, and the variations in the duration

of the convulsions were definitely greater than when unmodified shock treatments were applied (Chart 1). Because of the limited material and the fairly great variations, the declining curve was not smooth. The tendency for the duration to decrease is, however, clearly shown.

Table 2 shows that the difference between Shocks 1 and 2 was highly significant and was about 10 seconds. The remaining differences were smaller and not significant.

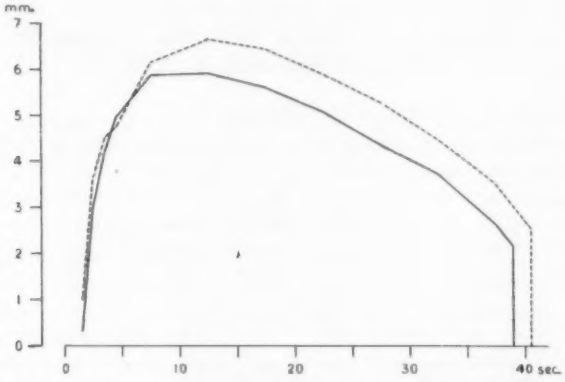


Chart 2.—Relative intensity of convulsions at the first shock (dotted line) and at the subsequent shocks (solid line) in a series of electric shock treatments. (Unmodified treatments, electromyographic recording of convulsions.)

TABLE 2.—*Duration of Convulsions (in Seconds) in a Series of Electric Shock Treatments in Connection with a Muscle Relaxant and Oxygen Administration*

| Shock No. | Duration of Convulsions | No. of Cases | Difference | *df* | *t* | *P* |
|---|---|---|---|---|---|---|
| 1 | 71.4 | 131 | | | | |
| | | | 9.56 ± 2.008 | 94 | 4.556 | < 0.001 |
| 2 | 61.4 | 120 | | | | |
| | | | 0.85 ± 1.575 | 95 | 0.540 | |
| 3 | 61.2 | 111 | | | | |
| | | | 3.27 ± 1.701 | 61 | 1.925 | |
| 4 | 58.0 | 79 | | | | |
| 5 | 59.6 | 48 | | | | |
| 6 | 54.6 | 21 | | | | |

C. *Measurement of the Convulsions by Means of an Electromyographic Method.*—In 39 cases where Shock 1 had been recorded it was compared with a subsequent shock, namely, with Shock 2 in 8 cases, with Shock 3 in 13 cases, with Shock 4 in 10 cases, and with Shock 5 in 8 cases. Unfortunately, it was not possible to investigate whole series of shocks. The entire material was taken together, and thus Shock 1 was compared with a subsequent shock, regardless of its successional number. The aim of the investigation was to ascertain whether the intensity of the convulsions and the frequency of the clonic jerks varied in the same way as the duration of the seizure, i. e., were most pronounced in the first treatment and decreased during the subsequent treatments. All treatments were unmodified.

The total duration of the convulsions (Table 3) was somewhat longer for Shock 1, but the difference was not significant. The difference was limited to the clonic phase, while the duration of the tonic phase was not appreciably changed. None of the differences was significant.

The intensity of the convulsions is shown in Table 3. The peak intensity of the convulsions was significantly higher for Shock 1, and the subsequent decrease amounted to nearly 10%. The energy generated above a given, medium level (4 mm. height of convulsion curve) was 32% less in the later shocks; this difference was highly significant. For every 5-second period during the seizure, starting from 10 seconds after the initiation of the seizure, there was a significant difference in intensity between Shock 1 and the subsequent shocks (Chart 2).

TABLE 3.—*Comparison Between the First and Subsequent Shocks in a Series of Electric Shock Treatments (Unmodified Treatments, Electromyographic Recording of Convulsions)*

| | | Shock No. 1 | Subsequent Shocks | Difference | *df* | *t* | *P* |
|---|---|---|---|---|---|---|---|
| Duration of convulsions | Tonic phase | 14.19 | 14.03 | 0.17 ± 0.413 | 38 | 0.405 | ..... |
| | Clonic phase | 26.37 | 24.91 | 1.47 ± 0.863 | 38 | 1.703 | ..... |
| | Total seizure | 40.50 | 38.93 | 1.62 ± 0.833 | 38 | 1.945 | ..... |
| Intensity of convulsions | Peak intensity | 7.03 | 6.39 | 0.64 ± 0.190 | 38 | 3.356 | < 0.01 |
| | Energy output above 4 mm. level | 11.99 | 8.19 | 3.79 ± 1.114 | 37 | 3.403 | < 0.001 |
| | Intensity during the 10-15 sec. period | 6.56 | 5.99 | 0.57 ± 0.152 | 38 | 3.730 | < 0.001 |
| | Intensity during the 15-20 sec. period | 6.37 | 5.57 | 0.96 ± 0.192 | 38 | 4.975 | < 0.001 |
| | Intensity during the 20-25 sec. period | 5.73 | 4.96 | 0.77 ± 0.245 | 38 | 3.147 | < 0.01 |
| | Intensity during the 25-30 sec. period | 4.96 | 4.24 | 0.87 ± 0.237 | 34 | 3.669 | < 0.001 |
| | Intensity during the 30-35 sec. period | 4.59 | 3.70 | 0.93 ± 0.360 | 27 | 3.552 | < 0.01 |
| Frequency of clonic jerks per 5 seconds | During 15-20 sec. period | 18.76 | 18.56 | 0.64 ± 0.361 | 27 | 1.782 | ..... |
| | During 20-25 sec. period | 16.29 | 15.34 | 1.08 ± 0.242 | 36 | 4.474 | < 0.001 |
| | During 25-30 sec. period | 13.24 | 12.47 | 1.18 ± 0.282 | 33 | 4.178 | < 0.001 |
| | During 30-35 sec. period | 10.48 | 9.47 | 1.04 ± 0.173 | 27 | 5.980 | < 0.001 |

The frequency of the clonic jerks (Table 3) was also lower for the later shocks than for Shock 1. This difference was highly significant for the whole clonic phase, except for its initial stage.

## COMMENT

The investigations that were conducted showed clearly that the successive decrease of cerebral excitability, which had been previously observed in connection with series of electric shock treatments, is also accompanied by changes in the duration and the intensity of the convulsions and in the frequency of the clonic jerks. The difference between the first and the second shock in a series is particularly pronounced; and it is probable that the inhibitory effect accumulates subsequently until stabilization takes place.

In all probability, these reactions have a reciprocal connection and are due to a functional change in the brain, perhaps a change in the fluid balance. After a series of shock treatments, at times, a microscopic examination shows the presence of cerebral edema (*inter alia* Hartelius[8]). It is well known that hydration reduces cerebral excitability. According to Toman and Goodman,[4] this is connected with

a reduction of the extracellular electrolyte concentration. At any rate, the cause must apparently be looked for outside the nerve cells, the refractory periods of which are very much shorter than those in question here.

There is also a practical side to this question. It is evident that the greater intensity of the convulsions during the first shock treatment in a series makes this most dangerous for the skeleton. If no fracture takes place during the first shock treatment, there is probably little risk of fracture occurring later, provided that the shocks are administered in a fairly continuous sequence, so that the moderating effect of the preceding treatments does not have time to wear off. When muscle relaxants are administered in connection with the shock treatments, if possible, a sufficiently strong dose should be given at the first treatment.

## SUMMARY AND CONCLUSIONS

By measuring the duration of the convulsions for 1,666 unmodified electric shock treatments and for 510 electric shock treatments in connection with a muscle relaxant and oxygen administration, it was shown that the duration was longest for the first treatment of a series, and that the duration then successively decreased; the decrease was most noticeable at the beginning of a series.

By means of an accurate electromyographic technique, it was clearly shown that also the intensity of the convulsions and the frequency of the clonic jerks were highest for the first treatment.

These effects, and the successive decrease of cerebral excitability, which has been previously observed, are considered to be connected with hydration or some other extracellular change occurring in the brain.

From a practical point of view, it is perhaps worth while to point out that the intensity of the convulsions and consequently the risk of fractures are greatest during the first shock treatment of a series.

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# ISONIAZID TREATMENT OF PSYCHIATRIC PATIENTS

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IT HAS BEEN observed that many patients treated for tuberculosis with isoniazid develop a feeling of well-being and an increase in appetite and weight. Whether this is secondary to a beneficial effect on the tuberculous process itself or is due to a direct effect on the personality has not been established. That isoniazid has a stimulating, and in some cases an irritant or toxic, effect on the nervous system, however, is well known.

In higher doses, 0.4 gm. per day or more, isoniazid frequently produces toxic effects on the nervous system. These are manifested by twitching of the muscles, hyperreflexia, palpitation, dizziness, difficulty in micturition, alterations in the electroencephalogram, convulsions, headaches, fatigue, or peripheral neuropathy with paresthesias and weakness.

The effects of isoniazid on the personality are more indefinite and difficult to evaluate. They range all the way from subtle changes in temperament to psychosis. Irritability, anxiety, depression, apprehension, tension, euphoria, insomnia, increase in libido, somnolence, sedation, restlessness, and mental confusion have been observed in varying and mixed degrees. These changes are not necessarily related to dosage but often are associated in some way with the underlying personality or with an idiosyncrasy to the drug.

The fact that isoniazid affects the nervous system and the personality has naturally suggested the possibility of its use, therapeutically, in psychiatric cases. In January, 1953, the coincidental improvement in the mental, as well as the physical, condition of tuberculous mentally ill patients being treated with isoniazid was reported.[1] Further studies failed to substantiate the initial impression of benefit in these cases. Wilson [2] treated 20 nontuberculous mental patients with isoniazid, with improvement in only one patient, who he believes would have recovered anyway. Salzer and Lurie,[3] on the other hand, found that 28 of 41 depressed patients improved on isoniazid. Delay [4] has also reported the favorable effect of isoniazid in patients with depression or melancholia. In evaluating the results of isoniazid in depression, it should be noted that most of these patients recover spontaneously from each attack.

Because the possible use of isoniazid in the treatment of psychiatric patients has not been extensively investigated, I have tried it in 65 such patients during the past eight months. The dosage averaged from 50 to 100 mg. three times a day. Patients were instructed to take their medication after meals because it sometimes causes gastric distress. The tolerance to isoniazid in psychiatric patients varies tremen-

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dously. Some of the patients became jittery or dizzy or developed insomnia or palpitation on as little as 50 mg. twice a day for one or two days. Other patients noticed no effect on 600 mg. a day.

Undesirable side-effects from isoniazid were frequently noted in this series of patients. They consisted, in order of frequency, of nervous tension or jitteriness, gastric distress, lightheadedness, fatigue, palpitation, insomnia, mental confusion, and paresthesias. Thirty-two of these 65 patients had to discontinue isoniazid because of side-effects, which usually appeared within two or three days after the beginning of treatment. Because of its stimulating effect, patients with anxiety tension were least tolerant to the drug. Of the 33 patients who were able to tolerate the drug and took it for at least three weeks, only 13 showed any beneficial effects, as is illustrated in the accompanying Table.

When analyzed in greater detail, these results were even less impressive. Many of the patients who improved would have improved anyway and continued to do so even though the isoniazid was discontinued. Only 8 patients in this entire series of 65 cases, after being on and off the drug several times, thought that it helped and continued taking it of their own volition. Of these eight patients, one was a migraine patient with fatigue, two were patients with a mild chronic, retarded type of schizophrenia, two were patients with the fatigue symptom of neurasthenia, and three were patients with depression.

*Results of Isoniazid in Sixty-Five Psychiatric Patients*

| Reaction Types and No. of Cases | Discontinued Because of Side-Effects | Unimproved | Improved |
|---|---|---|---|
| Depression, 17 | 7 | 4 | 6 |
| Schizophrenia, 14 | 7 | 4 | 3 |
| Anxiety, 13 | 10 | 3 | 0 |
| Neurasthenia, 10 | 4 | 3 | 3 |
| Organic, 7 | 3 | 4 | 0 |
| Migraine, 4 | 1 | 2 | 1 |

## SUMMARY AND CONCLUSIONS

Of 65 psychiatric patients treated with isoniazid, only 8 showed any improvement that seemed to be definitely related to the drug or its suggestive effect. The effect of isoniazid on the personality is varied and unpredictable, but in general it appears to be that of a stimulant in smaller doses and of a neurotoxin in larger doses.

Isoniazid is of very limited, if any, value in the treatment of psychiatric patients. It occasionally seems to help overcome fatigue, mental sluggishness, or depression associated with any of the various reaction types.

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# SIMPLE METHOD FOR RECORDING CURRENT AND VOLTAGE IN ELECTROCONVULSIVE SHOCK

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IN ANY attempt to evaluate the effects of electroconvulsive therapy or to elucidate the mechanisms involved in ECT, it is believed that the parameters of the stimulus should be known. A familiarity with the conflicting results reported in the field of electroshock research leads one to suspect that one of the serious deterrents to duplicating the work of another investigator is the lack of precise information regarding the quantitative values of the stimuli used by each investigator. In this field of research the usual practice is for the stimulus to be reported in terms of the stimulus duration and the current or voltage preset on the electroshock apparatus before the treatment. From our experiments in direct recording of the stimulus components, we have learned that the value of the stimulus as preset on the machine bears little relation to the amount of stimulus actually delivered to the subject (or tissue). Many factors underlie this discrepancy, a few examples of which may be cited: (1) whether or not there is good, constant contact between the patient and the electrodes; (2) the type of electrodes used; (3) the location of the electrodes on the subject or tissue under study, and (4) the accuracy of the electrical apparatus used to deliver the stimulus.

Since stimuli of different intensities do not usually produce the same results, it is believed that no really accurate comparison of related investigations in electrostimulation and electroshock is possible until some method is adapted to this type of research, by means of which precise data regarding the stimulus can be cited. A method is described in this report for monitoring the voltage and current actually delivered to the patient during electroconvulsive therapy. This method of direct recording of voltage and current has been used in experimental inquiries in this laboratory for a period of two years and has been found to have the advantages of simplicity of operation, accuracy, and compactness.

Any two-channel direct-writing oscillograph can be used. We have used a two-channel Brush oscillograph in some experiments, and in others we have used two channels of an Offner six-channel dynograph recorder. The data presented in this paper pertain to the Brush direct-writing oscillograph.

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The oscillograph was connected between the output of an Offner Type 733 electrotherapy apparatus and the patient electrodes. The oscillograph was so adapted that one channel would record the stimulating current and the other the voltage.

The schema in Figure 1 indicates how the two recording channels are connected. There is a resistor in parallel with the current recorder to reduce the sensitivity to a convenient scale. The value shown yields a full-scale range of 500 ma. (r. m. s.). Also, a voltage divider must be provided to reduce the sensitivity of the voltage channel to a full-scale range of about 150 volts r. m. s. The 15,000-ohm resistor also acts as a dampening resistor for the recording oscillograph. The values of these resistors may be modified for different ranges.

With the connection illustrated one correction may be applied to the current channel. The latter records the current through the patient and, in addition, the current through the voltage channel of the oscillograph. The current taken by the voltage channel is 7.7 ma. (r. m. s.) when a voltage of 150 volts is being recorded. In practice this extra current is a small percentage of the patient current (1.3% of

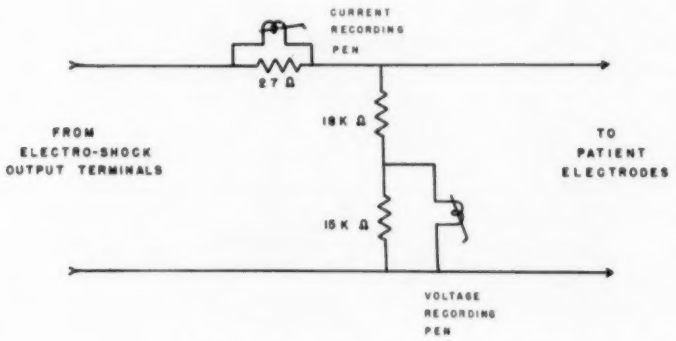


Fig. 1.—Schema of current-voltage recorder.

the patient current at 350 ma. and 90 volts) and may, for most purposes, be neglected. However, for more critical work the current through the voltage channel can be calculated from Ohm's equation:

$$I = E/R$$

where $E$ is the voltage to the patient and $R$ is the resistance of the voltage-measuring channel, including the voltage-dividing resistors. The patient current may be considered to constitute the difference between the measured current and this voltage channel current.

An alternative to the above method would be to connect the current channel so as to record patient current only, while the voltage channel would measure the sum of the patient voltage and that of the recording channel. However, under these conditions, the percentage error of the voltage channel would be relatively large (11% at 350 ma. and 80 volts). Thus, the first-mentioned method appears preferable.

Owing to individual variations in oscillograph sensitivity, it is necessary to calibrate the instrument used. An alternating current milliammeter and an alternating current voltmeter of sufficient range are used for this purpose. The milliammeter is connected in series with a light bulb, and the voltmeter is connected across the bulb's

terminals. The oscillograph, meters, and light bulb may be energized from the power line directly. Since the oscillograph deflection is linear with respect to input voltage, a single calibration will suffice.

The familiar 110 line voltage is actually the root mean square (r. m. s.) value of a voltage varying from 0 to + 144 volts, back to 0, down to — 155 volts, back to 0, etc., in a sinusoidal manner. Alternating current meters are usually calibrated in r. m. s. units; consequently, the bulk of the electroconvulsive shock nomenclature regarding the stimulus refers to the r. m. s. value. When the recording oscillograph is used, the pens record a "peak-to-peak" tracing, as illustrated in Figure 2. However, the value of this deflection will correspond to that of the meter from which it was calibrated. Therefore, the records can be reported in the usual r. m. s. units.

It is absolutely essential that none of the recording connections or terminals become grounded. Such might prove hazardous to the patient.

The recorder described is capable of perfect reproduction of 60-cps alternations of current. In addition to recording the amplitude of the stimulus, it is possible to

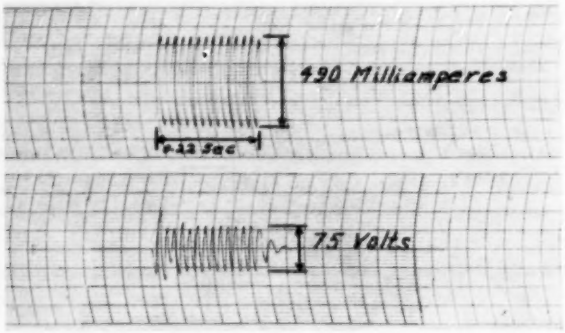


Fig. 2.—Sample record of electroshock stimulus recording.

observe the number of cycles of the current and thus to calculate the duration by substituting in the equation:

$$t = n/f$$

where $t$ is the duration of the stimulus in seconds, $n$ the number of cycles recorded, and $f$ the frequency of the stimulus. Since the usual stimulating frequency is the accurate 60-cps power line frequency and since it is possible to read the number of cycles recorded to within ¼ cycle, one may calculate the duration of the stimulus to within 4.2 msec. (1/240 second).

This method of recording the stimulus makes it possible to observe certain characteristics of the stimulus not usually noted. For example, any adventitious quantitative crescendo effect readily becomes apparent. Again, the synchronized recording of voltage and current makes it a simple matter to calculate the electrical impedance offered by the patient. If the current and voltage tracings are in phase with each other, the impedance offered is purely resistive and may be calculated by dividing the voltage by the current (Ohm's law). If, however, the voltage tracing should lead or lag behind the current tracing, it would indicate an impedance both resistive and reactive in nature. The degree of lagging or leading is a measure of the extent of the reactive component of the impedance.

# HISTAMINE TOLERANCE IN SCHIZOPHRENIA

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THE HISTORY of the use of histamine as a therapeutic weapon in the treatment of mental illness goes back for a number of years. Prior to that it had been used in general medicine for the treatment and alleviation of a number of conditions, for its properties as a vasodilator, and for its effect on gastric secretion. The doses employed have been small, usually about 0.5 mg. and never more than 1 mg.

In 1935 Gildea, Himwich, Hubbard, and Fazikas treated three catatonic schizophrenics, using histamine in sufficient doses to produce flushing and pupillary dilation.[1] No beneficial results were observed. In 1938 Marshall and Tarwater reported good results from the use of histamine in gradually increasing doses in a series of 36 psychotics.*

They regarded this as a nonspecific form of desensitization. Their patients became more cooperative and their appetites improved, but they tended to relapse after two months. Robinson, in a discussion on this paper, considers that the histamine improved brain metabolism by increasing the vascular supply.

Hill, in England, has published a number of papers, and even a small book, on the use of histamine combined with insulin as a form of "shock therapy." † The histamine doses used were stated to be 0.5 mg. on an average, while 2 to 8 mg. are described as poisonous doses.

Insulin in doses of 20 units was given simultaneously, apparently to counter any toxic reactions from the histamine.

Hill's rationale is obscure. He speaks of histamine acting as a metabolic stabilizer and at the same time appears to feel that its vasodilating properties are beneficial in some way. It is not clear whether the dosage figures that he quotes refer to histamine phosphate or histamine base. The phosphate is generally used, 3 mg. of histamine phosphate being equivalent to 1 mg. of the base. In our work we used the phosphate but give our doses in terms of the base.

In 1940 Robb, Kovitz, and Rapaport treated a small series of cases with rising doses of histamine phosphate (histamine acid phosphate) with the object of producing "vascular shock." [7] The highest dose used was equivalent to 2.5 mg. of histamine base. Improvement was slight and comparable to results in similar patients obtained with pentylenetetrazol (Metrazol) and amobarbital (Amytal) sodium.

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Saskatchewan Committee on Schizophrenia Research; supported by the Department of National Health and Welfare, Canada.

* References 2 and 6.

† References 3 through 5.

All patients in the series were long-stay cases, and 10 were catatonic schizophrenics.

In 1949 the Sackler brothers and van Ophuijsen published the results of treating 38 assaultive female patients at the Creedmoor State Hospital.[8] The cases were very mixed as to age, duration of stay, and clinical symptoms. A dose of 3 mg. of histamine base was used in all cases, though sometimes this amount was given over a period of some hours. In some instances vascular shock is reported to have occurred.

Of the group of 38 who received treatment, 28 showed some improvement and 5 were paroled. In a later paper, it was stated that of those patients who failed to respond to histamine a significantly greater number later improved with electric convulsion therapy (ECT), as compared with a control group that received ECT but no histamine.[9]

Rather similar are the experiences of Gunter, who in 1952 published an account of treatment with histamine in two small groups of cases.[13] The first, a group of three paranoid schizophrenics with illnesses of 5 to 11 years' duration, showed no response to histamine phosphate given twice daily for five weeks in doses rising from 3 to 7.5 mg. (1 to 2.5 mg. of histamine base).

A second group of patients received a course of injections rising rapidly to 7.5 mg. of histamine phosphate for 24 days. The duration of illness ranged from 1 month to 10 years. Nine patients were schizophrenics, and one suffered from involutional melancholia. A numerical rating scale was used to assess and record the degree of improvement quantitatively. Four catatonic patients showed a significant improvement, and four other schizophrenics who failed to respond to the treatment later reacted favorably to ECT, to which they had previously been refractory.

The Sacklers published a paper in 1951 in which they outlined their latest technique.[10] This consisted of giving rising doses of histamine until the systolic blood pressure had fallen to 50 or 60 mm. Hg and the diastolic blood pressure to 0. Half an hour after the first, a second injection could be given. Once a dosage level that caused a fall in blood pressure to 60/0 had been attained, it was maintained for 24 sessions, two injections being given with an interval of 30 minutes between them. It seemed that the histamine was effectively destroyed or neutralized in the space of half an hour. Vasomotor shock was countered by the injection of 0.5 to 1 cc. of 1 : 1,000 epinephrine intravenously. Pulse and blood pressure readings were carefully made at five-minute intervals.

In 1952 Hoch [12] sponsored a large-scale clinical trial of histamine therapy. Three mental hospitals in the United States tried it out, using the Sackler technique. Results were uniformly disappointing. It is interesting to note, however, that each hospital used a different-sized treatment group, with quite different numbers in each diagnostic category. One hospital included two hysterics; another, two organic cases. Only one hospital ran a control group. From the presentation of the results it would appear that each hospital used quite different evaluation criteria and had no standardized method of assessing the degree of improvement. It is not stated what doses of histamine were used in any of these trials, but the Sacklers mention having given up to 7 mg. of histamine base.‡

In a paper presented at a regional meeting of the American Psychiatric Association at Montreal in December, 1953, Rouleau and his co-workers reported on a series.

‡ References 8 through 10.

of 100 schizophrenics of both sexes, with a duration of illness of from 6 months to 14 years, who had been treated with histamine injections according to the Sackler methods.§ The authors found that 20 patients lost their florid symptoms sufficiently to be able to leave the hospital, though they remained essentially schizoid in attitude and did not all lose their hallucinations. It seems that all those patients who were paroled were early cases, with manifest signs of illness of from 6 to 11 months' duration. The remaining 80 patients, who had been ill from 2 to 14 years, remained substantially unaltered with three exceptions, who showed some improvement.

Twenty histamine-treated patients later received ECT. One only showed a marked improvement; five were slightly improved. Insulin coma therapy produced but a temporary remission of very short duration in one case.

These workers remark on the high tolerance that many schizophrenics have for histamine. They found that the mean dose for their group was 10 mg., with a maximum of 14 mg. at a single injection. This is the largest amount of histamine hitherto recorded, with the exception of that communicated in a preliminary report on the work to be mentioned below, which report was presented at the 1953 meeting of the Canadian Psychiatric Association at Winnipeg.[16]

At the beginning of 1952 we commenced a clinical trial on our own account in Saskatchewan. This arose out of a broadly based investigation into the problem of schizophrenia, and we were interested to see what effect histamine would have on the course of the illness. The trial was commenced by Hoffer and Parsons (1953), working at the Munroe Wing of the Regina General Hospital.

The patients all had mild and early schizophrenia, and only two of them had had symptoms for more than one year. Another patient had had recurrent symptoms over four years but had been ill for only six months on this occasion. In all, 12 patients received treatment.

The Sackler technique was closely followed, and the side-effects observed were similar to those which these authors have described in their papers. It was found that 2.0 to 6.5 mg. of histamine base was needed to lower the blood pressure to 60 mm. Hg systolic. Of the 12 patients treated, 4 failed to show any improvement. Eight showed a good initial improvement, but half of these had relapsed a year later.

While this trial was proceeding, a trial was started at the Saskatchewan (Psychiatric) Hospital at Weyburn on a series of chronic schizophrenic males, using an equal number of controls that had been selected at random from the entire group. This trial was never completed, for the simple reason that the supplies of histamine ran out; and only four patients received a four-week treatment, with no clinical improvement.

The four patients had been in the hospital for 1½ years, 16 years (two cases), and 20 years. The patient who had been ill for one and one-half years had had symptoms for no more than two years. They respectively tolerated 17.5, 15, 25, and 25 mg. of histamine base. One patient would probably have tolerated more, for his systolic blood pressure was still above 60 mm. after he had received 50 mg. of histamine in the course of an hour. The patient who tolerated 17.5 mg. had a pres-

§ Rouleau, Y.; Nadeau, G.; Delage, J.; Coulombe, M., and Bouchard, M.: An Appraisal of Histamine Therapy in Schizophrenics, presented at the American Psychiatric Association Regional Meeting, Montreal, in December, 1953.

sure still above 60/0 but was rendered extremely uncomfortable by severe precordial pressure (one of the noted side-effects in some cases).

Our first reaction to this strange occurrence was to conclude that some deterioration had taken place in the sample of histamine that we were using, and we returned it to the firm which had supplied it. This firm had provided us with two strengths of histamine, one having the equivalent of 1 mg. of histamine base per cubic centimeter, the other 5 mg. per cubic centimeter. Representatives of this firm had expressed misgivings when asked to manufacture the stronger material, as they felt that its use would be hazardous in the extreme. It turned out that the samples were

TABLE 1.—*Acute Schizophrenic Group*

| Name | Age | Duration of Illness, Mo. | Histamine Tolerated, Mg.* |
|---|---|---|---|
| M. B. | 33 | 12 | 6.5 |
| R. M. | 46 | 2 | 4.75 |
| T. T. | 15 | 1 | 5.5 |
| J. F. | 34 | 12 | 5.0 |
| A. P. | 23 | 6 | 2.75 |
| M. F.† | 33 | 6 | 6.0 |
| M. Y. | 22 | 3 | 3.0 |
| A. A. | 39 | 12 | 6.5 |
| M. Z. | 24 | 12 | 2.75 |
| M. F. | 24 | 12 | 5.25 |

* Average tolerance for group = 4.8 mg. of histamine base.
† = Recurrent symptoms for two years, but recent illness commenced six months ago.

TABLE 2.—*Schizophrenic Group 1, Ill for Five to Ten Years*

| Name | Age | Height | Weight, Lb. | Histamine Tolerated, Mg.* | Diagnostic Category |
|---|---|---|---|---|---|
| W. H. | 35 | 5'10½" | 173 | 20 | Catatonic |
| A. D. | 32 | 5' 8" | 198 | 12 | Hebephrenic |
| G. J. | 38 | 5' 6⅜" | 148 | 14 | Catatonic |
| S. B. | 40 | 5' 7¾" | 148 | 8 | Catatonic |
| L. M. | 40 | 4' 9½" | 102 | 6 | Hebephrenic |
| C. B. W. | 41 | 5' 2½" | 118 | 18 | Simple |
| D. K. | 31 | 5' 4½" | 120 | 7 | Catatonic |
| V. B. | 35 | 5' 6⅜" | 103 | 6 | Simple |
| E. C. | 34 | 6'10½" | 182 | 7 | Catatonic |
| A. H. | 53 | 5'11" | 192 | 11 | Unspecified |

* Average tolerance for group = 11.1 mg. of histamine base.

as active as ever, and the manufacturer was not a little astonished when told what quantities we had been using.

It seemed clear that some schizophrenics were able to tolerate much larger doses of histamine than normal individuals, and that schizophrenics of long standing were evidently able to take much greater doses than those who had been ill for a short time.

We therefore determined to try to repeat our findings on a larger scale in order to see to what extent ability to tolerate large quantities of histamine might correspond with the duration of illness. In particular, we were interested to see the reactions of those very chronic patients who are often referred to as "burned-out schizophrenics," that is, those members of the mental hospital population who have lost their earlier

florid symptoms and do not exhibit delusions, hallucinations, or marked vagaries of conduct. They remain solitary, disinterested, and apathetic. The questions that often arise are whether the original disease process is still active or whether it has ravaged and gone its way, and whether the patient's present state is the result of this disease, which is now no longer active, or the result of prolonged residence in an institution.

For this new trial, 40 male schizophrenics at Weyburn were selected at random and divided into four groups of 10 each. The groups comprised (1) patients who had been ill for more than 5 years and up to 10 years (Table 2); (2) those who had

TABLE 3.—*Schizophrenic Group 2, Ill for Ten to Fifteen Years*

| Name | Age | Height | Weight, Lb. | Histamine Tolerated, Mg.* | Diagnostic Category |
|---|---|---|---|---|---|
| E. B. | 33 | 5'10" | 165 | 8 | Catatonic |
| C. C. | 33 | 5' 3" | 124 | 24 | Hebephrenic |
| F. D. | 54 | 5' 4¾" | 120 | 5 | Paranoid |
| I. H. | 32 | 5' 6½" | 128 | 18 | Catatonic |
| J. H. | 43 | 5' 6½" | 128 | 15 | Hebephrenic |
| M. H. | 37 | 5' 7¼" | 160 | 10 | Catatonic |
| A. S. | 44 | 5'10" | 137 | 10 | Paranoid |
| M. S. | 34 | 5'10¾" | 140 | 10 | Hebephrenic |
| J. S. | 33 | 5' 8" | 170 | 8 | Unspecified |
| N. Z. | 31 | 5' 5" | 120 | 8 | Unspecified |

* Average tolerance for group = 12.0 mg. of histamine base.

TABLE 4.—*Schizophrenic Group 3, Ill for Twenty to Twenty-Five Years*

| Name | Age | Height | Weight, Lb. | Histamine Tolerated, Mg.* | Diagnostic Category |
|---|---|---|---|---|---|
| W. A. | 52 | 5' 9½" | 136 | 28 | Unspecified |
| C. B. | 52 | 5'10½" | 158 | 17 | Unspecified |
| V. B. | 49 | 5' 4" | 223 | 7 | Unspecified |
| A. D. | 55 | 5'10" | 128 | 6 | Paranoid |
| A. M. | 46 | 5' 7" | 254 | 22 | Hebephrenic |
| O. M. | 47 | 5' 8¼" | 140 | 20 | Hebephrenic |
| C. H. | 45 | 5' 7¾" | 206 | 16 | Simple |
| F. D. | 52 | 5' 7¼" | 164 | 11 | Simple (on basis of primary defect) |
| F. R. | 39 | 5' 4" | 144 | 16 | Hebephrenic |
| F. H. | 42 | 5' 7" | 134 | 11 | Unspecified |

* Average tolerance for group = 15.4 mg. of histamine base.

been ill for more than 10 years and up to 15 years (Table 3); (3) those who had been ill for more than 20 years and up to 25 years (Table 4); and (4) those who had been ill for more than 25 years (Table 5).

Some patients in Group 4 had been ill for over 30 years, and two for 37 years; but patients over 60 years of age were excluded from the series. In addition to these four groups, a fifth group, consisting of nonschizophrenic patients who had been in the hospital for more than 10 years (Table 6), was also tested.

The assembly of a control group of 10 long-stay nonschizophrenic patients, even from a population of 1,000, proved rather difficult. As far as possible, patients selected were not more than 60 years of age. Cases of senility were excluded, as

most of these had sclerotic blood vessels. Epileptics were not selected, as there appears to be a certain connection between schizophrenia and epilepsy, in some cases at least, and it is proposed to make a special study of epileptics from this point of view at a later date. Low-grade mental defectives were not thought to be suitable, as a number of these may be deteriorated schizophrenics with onset in early childhood. In the end, the control group comprised three cases of manic-depressive psychosis (two manic and one depressed), five cases of nonactive dementia paralytica, and two high-grade mental defectives. The duration of stay was from 10 to 36 years (the last in the case of a 42-year-old moron who had been admitted at an early age).

Patients in Groups 1, 3, and 4 were given Hoffer's atropine test for schizophrenia. This test, which has been described by Hoffer,[14] consists of injecting 3 mg. of atropine sulfate and of observing the pulse and blood pressure at 5-minute intervals for 30 minutes. Normally, a rise in blood pressure begins 10 minutes from the time of injection and reaches a peak of 15 to 25 mm. Hg above the resting pressure. In schizophrenic and brain-damaged patients the blood pressure remains at the resting level or may drop.

TABLE 5.—*Schizophrenic Group III for Twenty-Five Years and Over*

| Name | Age | Height | Weight, Lb. | Histamine Tolerated, Mg.* | Diagnostic Category |
|---|---|---|---|---|---|
| E. R. | 50 | 5′ 6¾″ | 115 | 7 | Unspecified |
| J. G. | 55 | 5′ 6½″ | 124 | 20 | Unspecified |
| R. C. | 56 | 5′ 5″ | 126 | 12.5 | Hebephrenic |
| C. McL. | 50 | 5′10¼″ | 135 | 7.5 | Catatonic |
| N. McL. | 57 | 5′ 6″ | 140 | 6 | Hebephrenic |
| J. B. | 50 | 5′ 6¾″ | 150 | 20 | Hebephrenic |
| F. G. | 58 | 5′ 9½″ | 188 | 12.5 | Hebephrenic |
| G. M. | 56 | 5′ 6½″ | 135 | 5 | Hebephrenic |
| D. G. | 56 | 5′ 7⅝″ | 125 | 15 | Paranoid |
| O. R. | 55 | 5′ 6″ | 124 | 7 | Unspecified |

* Average tolerance for group = 11.25 mg. of histamine base.

As will be seen in Table 7, this test was positive in 70% of the cases in Group 1, 70% of the cases in Group 3, and 80% of the cases in Group 4.

Each patient was given a subcutaneous injection of histamine, and the pulse and blood pressure were checked at 10-minute intervals. After 30 minutes a second, larger injection was given. The test was repeated on each succeeding day, with an increased dose of histamine on each occasion until the systolic blood pressure had been reduced to 60 mm. Hg or below for two consecutive readings. There was a tendency for a rapid recovery after large doses. No attempt was made to obtain a diastolic pressure of 0.

Apart from the fall in blood pressure, side-effects in these patients, even after massive doses, were not remarkable.

Signs and symptoms of shock, as evidenced by pallor, sweating, and restlessness, tended to appear toward the limits of the patient's tolerance, but these were marked only in seven cases (17.3%) of the schizophrenic group and in three cases (33.3%) of the smaller, control group.

On a few occasions the blood pressure tended to fall still further after reaching the 60 mm. mark, instead of beginning rapidly to rise again after 10 minutes; but

2 cc. of 1 : 1,000 epinephrine given intramuscularly rapidly reversed this fall. Vomiting occurred on three occasions, each time in a different patient. Four patients (3 schizophrenics, 1 control) had an urge to defecate followed by a bowel evacuation. This happened at the limit of tolerance in three cases, and in one case (a schizophrenic) it took place each day after the 5 mg. mark had been reached and continued up to the patient's limit of tolerance, which was reached at 14 mg.

Pallor and sweating were generally observed once the dose had been increased beyond 6 mg., and after each injection there was usually an increase in the rate and depth of respiration, which subsided after 10 to 15 minutes. A short, dry cough often commenced after injection, and this might persist throughout the session. Expectoration was fairly frequent, probably due to the metallic taste induced by histamine.

Slight restlessness occurred in most cases. It was marked in five of the schizophrenics and in one of the controls. In some instances this seemed to be caused by the skin irritation caused by the vasodilatation. Strangely enough, headache was

TABLE 6.—*Nonschizophrenic Control Group, Hospitalized for Ten Years or Over*

| Name | Age | Height | Weight, Lb. | Yr. Hospitalized | Histamine Tolerated, Mg.* | Diagnostic Category |
|---|---|---|---|---|---|---|
| F. H..... | 61 | 5′ 6¼″ | 140 | 23 | 7 | Manic-depressive psychosis (manic) |
| N. F..... | 60 | 5′ 5″ | 138 | 24 | 4 | Manic-depressive psychosis (depressed) |
| J. G..... | 58 | 5′ 2¾″ | 148 | 15 | 4 | Dementia paralytica |
| M. L..... | 29 | 5′11¼″ | 165 | 16 | 10 | Manic-depressive (moron) |
| H. J..... | 52 | 5′11″ | 158 | 16 | 3.5 | Dementia paralytica |
| P. M..... | 62 | 5′ 5½″ | 140 | 18 | 12 | Dementia paralytica |
| L. Y..... | 58 | 5′ 4½″ | 140 | 21 | 6 | Dementia paralytica |
| L. B..... | 51 | 5′ 5½″ | 125 | 11 | 5 | Dementia paralytica |
| J. W..... | 63 | 5′ 7″ | 188 | 36 | 1.5 | Manic-depressive (manic) |
| L. D..... | 42 | 5′ 7½″ | 152 | 11 | 10 | Manic-depressive (moron) |

* Average tolerance for group = 6.4 mg. of histamine base.

complained of only in one instance (one schizophrenic, and in none of the controls), despite the fact that very severe headache is an almost invariable symptom when small doses are given. Most of the Regina patients complained of headache initially, but this ceased as the dose increased.

Precordial pressure was not observed in this series, though it was evidently a frequent occurrence in the Sackler cases, and was marked in one of the patients who originally received histamine therapeutically.

Tolerance to histamine varied widely in all patients in each group. It appeared to bear no relation to body weight or to the clinical type of schizophrenia (Tables 2 to 6).

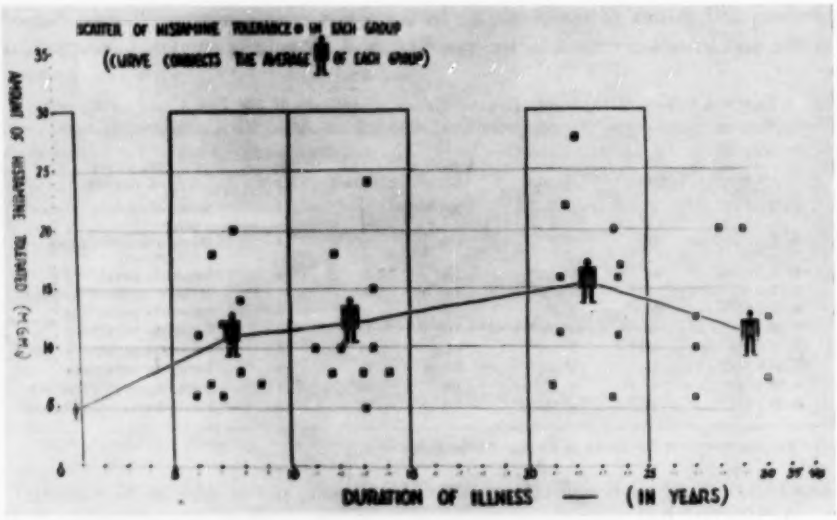
On the other hand, all the schizophrenics were able to tolerate large doses. The lowest amount tolerated by the schizophrenics was 5 mg., in two cases, and only five tolerated less than 7 mg., the highest dose hitherto reported. One patient even tolerated 28 mg. with no side-effects other than the fall of blood pressure. This is four times as great as the highest recorded dose of histamine.

Side-effects, particularly restlessness, dyspnea, and shock, were minimal in those patients whose blood pressure was affected only by the higher doses. In the entire

group of 40 chronic schizophrenics, 14 tolerated 15 mg. or more, and in all but 1 of these (who developed symptoms of shock at 24 mg.) side-effects were absent or only very slight.

As averages for all five schizophrenic groups, those who had been ill for less than a year (10 out of the 12 Regina cases) had an average tolerance of 4.8 mg.; those who had been ill for 5 to 10 years tolerated 11.1 mg.; those who had been ill for 10 to 15 years tolerated 12 mg.; those who had been ill for 20 to 25 years tolerated 15.4 mg., while those who had been ill for more than 25 years tolerated 11.25 mg.

The average tolerance of the rather mixed control group was 6.3 mg. This was greater than that for the early schizophrenic group, but markedly less than that of the 5- to 10-year schizophrenic group.




COMMENT

The accompanying Figure and Tables show beyond any shadow of doubt that patients with long-standing schizophrenia can frequently tolerate very large doses of histamine. The extent of the tolerance varies widely from case to case and appears to bear little relation to the age and body size of the patient or the clinical type of illness. It has frequently been shown that schizophrenics can tolerate abnormally high doses of drugs and hormones, such as insulin, thyroxin, and atropine, but the tolerance of some of the patients for a substance as toxic as histamine can only be described as "staggering."

It will also be noted (Figure) that when the average group tolerance is plotted, this rises up to the 20- to 25-year group and then declines, though it still remains high. In the long-standing cases, the lowest tolerance is as great as the highest value recorded for a normal individual or for any early case.

Although this result will require further investigation, it would appear that even at this early stage two conclusions can be drawn: 1. Chronic schizophrenics have a high tolerance to histamine, and some have an enormous tolerance. 2. The high tolerance persists for many years, thus suggesting that if this is connected in some way with the schizophrenic process, the schizophrenic process shows little decline after the lapse of many years, and that most "chronic" schizophrenics are still the

TABLE 7.—*Histamine Tolerance and Atropine Test*

| Name | Mg. of Histamine Tolerated | Atropine Test Finding |
|---|---|---|
| Group 1, 5 to 10 years of illness | | |
| A. H. | 11 | Schizophrenia |
| A. D. | 12 | Schizophrenia |
| G. J. | 14 | Schizophrenia |
| S. B. | 10 | Schizophrenia |
| D. K. | 7 | Atypical |
| W. H. | 20 | Schizophrenia |
| D. B. | 6 | Schizophrenia |
| C. W. | 18 | Atypical |
| L. M. | 6 | Schizophrenia |
| E. C. | 7 | Nonschizophrenia |
| 30% failure | | |
| Group 3, 20 to 25 years of illness | | |
| W. A. | 28 | Schizophrenia |
| C. B. | 17 | Schizophrenia |
| V. B. | 7 | Atypical |
| A. D. | 5 | Schizophrenia |
| A. M. | 22 | Nonschizophrenia |
| O. M. | 20 | Schizophrenia |
| F. H. | 11 | Nonschizophrenia |
| F. R. | 16 | Schizophrenia |
| F. D. | 11 | Schizophrenia |
| C. H. | 16 | Schizophrenia |
| 30% failure | | |
| Group 4, 25 and over years of illness | | |
| O. R. | 7 | Schizophrenia |
| D. G. | 15 | Schizophrenia |
| G. M. | 5 | Schizophrenia |
| E. R. | 10 | Schizophrenia |
| J. G. | 10 | Nonschizophrenia |
| C. McL. | 7.5 | Atypical |
| J. B. | 20 | Schizophrenia |
| F. G. | 12.5 | Schizophrenia |
| N. McL. | 6 | Schizophrenia |
| R. C. | 12.5 | Schizophrenia |
| 20% failure | | |

victims of their original illnesses rather than of "secondary dementia." The change is in the presenting symptoms rather than in the internal economy of the patient.

It will be noted, however, that the mean tolerance of the nonschizophrenic (control) group was also much higher than usual and even slightly surpassed the mean tolerance of the very early schizophrenic group. Even so, it was greatly below that of its schizophrenic contemporaries.

It might seem that, while schizophrenia of long duration produces some factor that induces resistance to large doses of histamine, a similar factor, though on a smaller scale, can also result from prolonged hospitalization.

It is clearly necessary to work out the histamine tolerance of other groups of patients suffering from other clear-cut psychiatric syndromes.

The exact nature of the factor causing resistance to histamine in schizophrenia can only be speculative at present. Fischer, in a recent paper, has postulated that the schizophrenic, as shown by his diminished responses to certain drugs, is in the resistant phase of the general adaptation syndrome.[15] He points out that this phase would take some time to develop and would therefore not be apparent in the early stages of the illness. On the other hand, it would tend to increase up to a point with the passage of time and show a decline after the lapse of many years. A considerable individual variation in the amount of resistance developed, both in time and in degree, might be expected.

Hoffer believes that the abnormal response of schizophrenics to atropine may be due to an abnormally high sympathetic tone, as shown by the failure of large doses of atropine to raise the blood pressure, and by their tendency, rather, to produce a fall. If this is so, the high tolerance to histamine might be explained by the fact that epinephrine (Adrenalin) and arterenol (Noradrenalin) exert a strongly antihistaminic action. It might be expected that patients in the resistant phase of the general adaptation syndrome would be producing large quantities of cortisone and other adrenal steroids, which also have a powerful antihistaminic effect.

Apter and Holstead have found that bilateral adrenalectomy does not influence the illness in long-standing schizophrenia.‖ It would be interesting to know the histamine tolerance of these adrenalectomized patients.

There seems to be a good deal of evidence to suggest that the histamine resistance of schizophrenics is a nonspecific reaction, but it is clear that a great deal more work must be done in order further to evaluate this rather remarkable finding.

It is interesting, though, to be able to report on another example of deranged metabolism in this illness, and it seemed justifiable to present the findings for what they are worth at this stage, as they do seem to add a little to our still woefully scanty knowledge of the biology of schizophrenia.

‖ Presented at the regional meeting of the American Psychiatric Association, Topeka, Kans., in October, 1953.

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# REACTIONS OF THE CAT PIAL CIRCULATION TO HYPOTENSIVE STATES INDUCED BY HEXAMETHONIUM BROMIDE

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SKULL window preparations have been used extensively since Forbes [1] introduced a satisfactory technique whereby a small section of the pial vessels can be observed and accurately photographed without the embarrassment of vessel movement or the disadvantage of any disturbance of internal pressure arrangements. Such a preparation allows the detailed study of vascular changes in an important area and has the advantage of displaying those vessels contributing appreciably to the peripheral vascular resistance and thus most likely to show significant changes in any circulatory readjustments. Unfortunately, no capillary bed is demonstrable and only a small superficial area is exposed; but there is evidence to suggest that the pial vessels reflect accurately the direction of changes in the whole brain (Finesinger and Putnam [2]), and some idea of the reactions of the deeper cerebral vessels can be gained from alterations in the general color of the field.

Direct observations on moving blood columns provide only gross indications of flow changes, as do alterations in the arteriovenous color differences. However, by serially measuring and correlating changes in arterial calibers with induced changes in the systemic blood pressure, an accurate qualitative impression of the pial vascular responses can be obtained. The significance of such changes must be assessed from consideration of Poiseuille's Law, according to which the resistance of any segment of a vessel is inversely proportional to the fourth power of its diameter, and at a constant pressure gradient the volume flow is directly proportional to the fourth power of this diameter.

With a modified skull window preparation the size and shape of the underlying pial vessels were studied and recorded by serial photomicrographs in hypotensive states induced by hexamethonium bromide and their calibers correlated with the blood pressures. Preliminary observations on similar states induced by blood loss and on various atypical arterial forms and arteriovenous connections were also noted.

## METHOD

Fourteen cats (2 to 3.5 kg.) were anesthetized, 9 with pentobarbital (Nembutal) alone and 5 with chloralose added. The head of the cat (lying horizontally prone) was immobilized erect by a jaw-holding clamp and a window fitted into a right parietal trephine opening, closely following Forbes's original technique. However, instead of his metal-framed externally threaded

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screw-in type of window, a Perspex plug of 1.3 cm. diameter was employed, a layer of wax on the external rim forming a watertight seal with the outside of the skull. Two needles just penetrating the window enabled all the air to be displaced by Ringer-Locke solution, or, if possible, by previously aspirated cerebrospinal fluid, before the needles were finally plugged and the whole left undisturbed for the rest of the experiment. No circulatory changes were induced until the window had been sealed for at least one hour, with control observations meanwhile.

The mean blood pressure was recorded continuously on a kymograph from the left brachial artery; the respiration (in eight animals only) from the side-limb of the previously inserted tracheotomy tube. The posture was unaltered, and the body temperature maintained constant.

The window was illuminated by water-filtered lamps, supplemented in later experiments by an electronic flash. To obtain a large field with good depth of focus a binocular dissecting microscope was used, with one eyepiece adapted for photomicrography. A magnification of × 40 was the usual practical maximum. Changes were assessed from comparable serial photographs rather than directly, so that the whole field could be followed instead of preselected vessels.

Hexamethonium bromide was administered intravenously, usually in initial doses of 3 to 5 mg. per kilogram; repeat doses and those at low pressure levels were often larger. These amounts were chosen to produce considerable rapid changes, thereby accentuating cerebral vascular reactions also; there appeared to be no pharmacological disadvantages (Paton [8]) in this high dosage level.

*Arterial Reactions to Hypotensive Episodes with Hexamethonium Bromide*

| Group | Fall in B. P., Mm. Hg | Range of Initial Mean Brachial B. P., Mm. Hg | | No. of Animals | No. of Observations | Arterial Reactions | |
|---|---|---|---|---|---|---|---|
| | | Maximum | Minimum | | | Dilatation | Unchanged |
| I | Exceeding 25 | 145 | 60 | 11 | 17 | 15 | 2 |
| II | 15 to 25 | 120 | 60 | 5 | 6 | 3 | 3 |
| III | Less than 15 | 120 | 40 | 12 | 30 | 2 | 28 |

## RESULTS

The reactions of 14 animals to initial and repeated administrations of hexamethonium bromide are shown in the accompanying Table, where, irrespective of the dosage used, they are classified as to the changes in mean arterial pressure into three groups—those showing a fall of blood pressure exceeding 25 mm. Hg (Group I), those with a fall of 15 to 25 mm. Hg (Group II), and those with a fall of less than 15 mm. Hg (Group III). These reductions in pressure were produced from varying levels of initial mean pressures lying between the limits as shown for each group.

The response was taken to be one of "dilatation," for the purposes of this table, when at least some of the arterial elements showed an increase in caliber, as illustrated in Figures 2 and 3. This proved necessary, since it was found that not all the arteries dilated uniformly, if at all, and in nearly half of the fields some vessels were apparently unchanged and remained so in repeated observations (Fig. 3). In addition, as is shown in both figures, certain fixed dilated fusiform arterial segments remained almost unaltered throughout the procedures, as they did also in exsanguination and asphyxial studies. Usually their entering and leaving vessels showed the general arterial dilatation responses (Fig. 2), but this was not so in some instances when the main trunk artery was little changed (Fig. 3). Reductions in arterial caliber were not seen, at least in the early phases of the pressure changes, except in

one animal, in which in repeated observations the arteries of a whole section of the field appeared unaltered or slightly smaller in hypotensive episodes, whereas the rest of the vessels dilated to a striking degree. These reactions were included in the "dilatation" responses in view of these predominant marked changes. In the Table no effort was made to assess the degree of change precisely, since it varied with different vessels and also along the length of the same vessel.

The fall in blood pressure was greater with initial doses and of longer duration, especially at the higher initial pressures often present with combined pentobarbital-chloralose anesthesia. Repeat doses shortly after the first dose or initial doses at

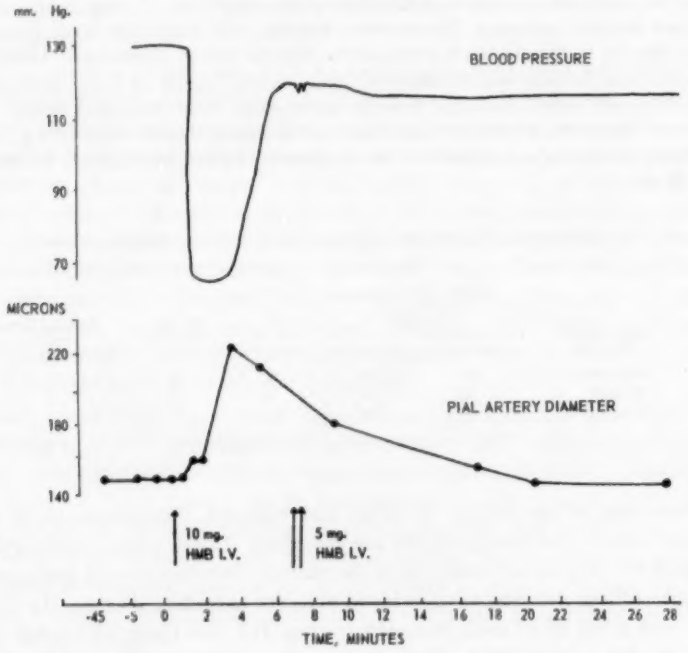


Fig. 1.—Changes in the blood pressure and caliber of an artery at one selected point with intravenous hexamethonium bromide (10 mg.), followed by two 5 mg. doses. Cat 2.25 kg.; pentobarbital-chloralose anesthesia.

lower blood pressures produced usually transient smaller changes, if any at all, and made up nearly all the observations in Group III. Long-lasting slight falls were unaccompanied by detectable arterial changes as shown in Group III. Transient falls were, however, difficult to follow accurately, and, though in Group I they were usually associated with some dilatation, in both Groups I and II they made up most of the observations recorded as unchanged.

In six animals (10 observations) a sufficient number of photographs were taken to allow the satisfactory tracing of the precise time course of the changes and the plotting of the blood pressure and the caliber of one of the larger arteries at one fixed point (Fig. 1), it being appreciated that greater relative changes, but less

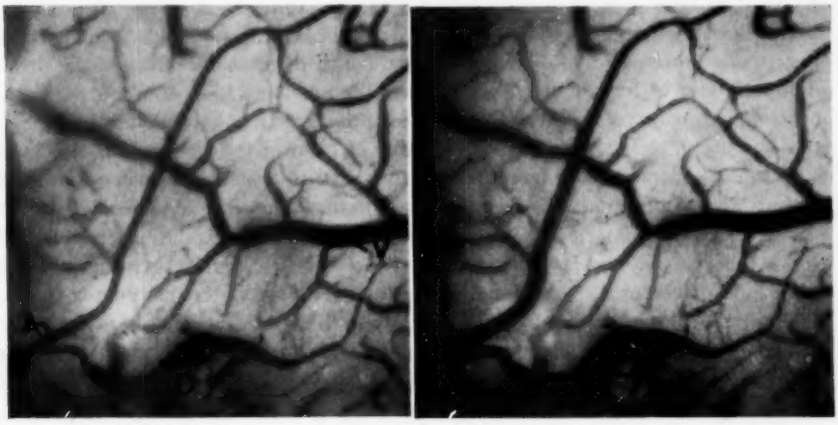

Fig. 2.—Pial vessel changes with hexamethonium bromide: left, before (mean brachial blood pressure 120 mm. Hg); right, after (mean pressure 105 mm. Hg). *A* indicates artery; *V*, vein; *D*, dilated arterial segment. Cat 2.75 kg.; pentobarbital-chloralose anesthesia, 10 mg. of hexamethonium bromide intravenously; × 25.

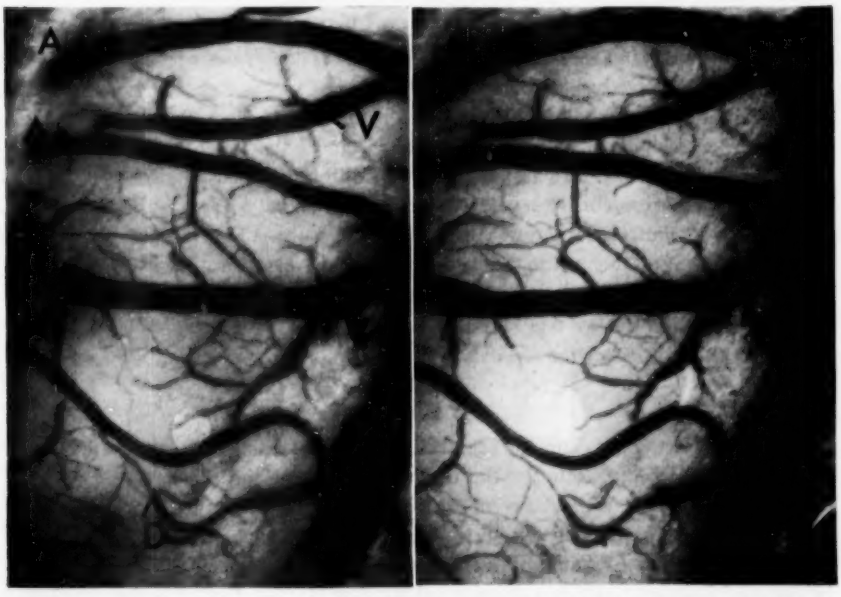


Fig. 3.—Pial vessel changes with hexamethonium bromide: left, before (mean brachial blood pressure 135 mm. Hg); right, after (mean pressure 115 mm. Hg). *A* indicates artery; *V*, vein; *D*, dilated arterial segment. Cat 3.25 kg.; pentobarbital-chloralose anesthesia, 10 mg. of hexamethonium bromide intravenously; × 25.

capable of precise measurement, might be present in smaller vessels. Figure 1 shows the usual findings in these animals and, indeed, in most of the observations in Group I. In general, with the intravenous administration of hexamethonium bromide there was usually within 10 to 15 seconds a sharp fall in the blood pressure of the order of 40 mm. Hg, with gradual restoration over the following 15 to 20 minutes. Commencing within approximately half a minute of the injection, but only after the pressure had begun to fall, there was a dilatation of most of the visible arterial vessels (200 to 20 $\mu$ diameter). This dilatation increased to a maximum when the blood pressure was just beginning to rise again (two to four minutes), and passed off as the pressure returned to normal, but usually before it had done so. Only 2 of these 10 closely followed episodes failed to show the lag of 10 to 15 seconds between the onset of the fall in blood pressure and the first detectable change in the pial vessels, and in both of these the pressure fall was much slower than usual and the vessel changes paralleled it *pari passu*. The apparent premature regression of the caliber changes before the restoration of the blood pressure was probably not due to the limitations of the technique in failing to detect the gradual passing off of slight changes (a possible criticism of all the observations on Group III), since in four animals (nine observations) the arteries in some areas assumed at a still slightly reduced pressure an even more constricted state than before the fall in blood pressure. In their hypotensive episodes, which had all been short, three had shown only slight dilatation, and in the fourth animal the vessels had been apparently unaltered.

The veins showed little caliber change during these reactions, only minor degrees of both narrowing and dilatation being observed. Though the venous flow was not closely followed directly, it appeared slightly slowed in some observations, but only temporarily in the initial stages of the hypotensive trough, when also, in one instance with a large precipitate fall, the blood drained out of the veins, leaving them transiently less well filled. The arteriovenous color difference was somewhat accentuated in these hypotensive episodes in association with some deepening of the general brain color. At times a large initial precipitate pressure fall was marked by a sharp gasp and attempts at vomiting, most frequently in association with venous flow changes, but this was also rather transient and there was no appreciable upset in the respiratory rhythm, save possibly a small variable increase in rate and amplitude. The general condition of the animals seemed unimpaired.

## COMMENT

The chief centers of interest are the mechanism of the changes, the adequacy with which they compensate for the lowered pressures, and the apparently varied reactive potentialities of the different arterial segments. The origin of the pial vessel changes is not certain, even though they are similar to what is thought to occur in other areas, in man (Arnold and associates,[4] Burt and Graham [5]), and in animals (Paton and Zaimis [6]). From extensive cat window studies, Forbes and co-workers [7] and Fog [8] concluded that the pial arterial response to any pressure fall was dilatation, though no explanation for this intracerebral compensatory mechanism could be satisfactorily established. Thus, the present changes might be produced similarly, rather than by the hexamethonium blocking of pathways maintaining arterial constriction. An important aspect of the distinction is that, whereas with a compensa-

tory mechanism no increase in the cerebral circulation might be expected from any associated procedure preventing the blood pressure fall, such as posture, drugs, or positive pressure applied to the limbs or trunk (Restall and Smirk [9]), on the contrary a valuable increase might be obtained by these procedures if the vascular cerebral reactions were primarily hexamethonium effects.

The wide range of initial pressures from which dilatation responses were elicited would seem to favor mechanisms other than those put forward by Forbes and co-workers,[7] who thought that there was a critical level below which dilatation occurred in response to slowed flow. However, the apparent lag of the pial changes behind those in other areas (as presumed from the preceding fall in blood pressure) suggests just such a compensatory mechanism. Nevertheless, similar delays occurred in the pial changes with direct stimulation of the cervical sympathetic (Forbes and Wolff [10]) and vagus nerves (Forbes and associates [7]). In addition, it might be possible to explain the lag in dilatation as a hexamethonium effect arising from differences in ganglion susceptibility (Paton [8]). Also, the degree of sensitivity of a ganglion to a blocking agent is greater at higher than at lower (Paton [8]) stimulation rates. Areas in which the constrictor tone was high could show greater relative initial changes, which, in rapidly reducing the blood pressure, might thereby mask the coincident similar but smaller pial changes and thus accentuate the delay in their appearance. With the decay of the action of the drug, such considerations could also explain the premature return of the pial vessels to their initial caliber before the complete restoration of the blood pressure and, similarly, the lack of pial change with small pressure reductions and possibly transient ones. However, the return of vessels at a still reduced pressure to a state more constricted than before the administration of hexamethonium is less easily accounted for, as is also the occurrence of the maximum vessel caliber on the rising phase of an appreciable hypotensive trough.

Additional, but incomplete, observations on other methods of reducing the blood pressure have not clarified the issue. Comparable pressure reductions were achieved by the method of applying suction to the lower abdomen and legs, as described by Restall and Smirk.[9] This technique produced rather similar pial dilatations, but the effect of this procedure was complex, including the serious possibility of associated respiratory disturbances. This criticism also might be applied to similar changes observed with the Veratrum alkaloid neogermitrine. However, hypotensive episodes with intravenous histamine did not seem to produce dilatations of a similar degree, nor did exsanguination studies necessarily favor an automatic compensatory mechanism, though it might have been masked by the constrictive reactions induced by blood loss. From such conflicting evidence it could not be established conclusively that hexamethonium produced directly the observed vessel changes.

Assessment of the adequacy of the dilatations in compensating for the lowered pressures was also difficult. Apart from the gasp and vomiting with the initial precipitous fall, the condition of the animals appeared unchanged. These reactions, which have been similarly noted in the human, may have been an expression of the observed lag in the dilatation with consequent transient cerebral anoxia and carbon dioxide accumulation. The slight slowing of flow in the relatively unchanged veins suggested reduction in the total flow, though not necessarily to a disadvantageous

degree, and so also did the impression of accentuation of the arteriovenous color differences. Some possible doubt was thrown on the validity of any indirect method involving oxygen or other gaseous uptake, in that the presence of direct arteriovenous connections was established on at least two occasions and in one the arterial limb was observed to dilate with a hypotensive episode.

No explanation can be offered for the apparent differences in reactivity of the pial arterial elements. It might be argued that for a vessel to remain unaltered at a lower distending pressure the tone must have been relaxed, though not sufficiently to produce dilatation or thereby alter the resistance. The problem would then be one of degrees of reactivity rather than the absence of it in some areas, and this might be a partial explanation for the lag in vessel change behind the fall in blood pressure. Mechanical interference from operative procedures could perhaps be responsible for the observed differences as also for the dilated fixed segments, but alternatively it seemed not impossible that there were structural and functional differences in various pial arterial segments, perhaps with associated specialization in innervation accounting for these observations.

## SUMMARY

Through skull windows in 14 cats observations, direct and photographic, were made on the pial circulation, and the vessel calibers were correlated with blood pressure changes induced by intravenous hexamethonium bromide.

Dilatation of at least some of the pial arteries was associated with most pressure falls exceeding 25 mm. Hg; it was present in half of the trials showing falls of 15 to 25 mm. Hg; it was usually absent with falls of 15 mm. Hg or less.

The arterial changes began after the commencement of the fall in blood pressure, were usually maximal when it was rising again, but passed off before the blood pressure was quite restored.

Differences in outline and in degree of change were noted in arterial segments. The veins were relatively unaltered.

The origin, adequacy, and localization of the changes are discussed.

Prof. J. E. Caughey, Prof. A. McIntyre, Dr. E. K. Macleod, and Prof. F. H. Smirk gave advice and assistance; Dr. W. Ritchie Russell, C.B.E., criticism of the text. The work was carried out with a grant from the Medical Research Council of New Zealand.

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# VALIDITY OF ARCHIMEDES SPIRAL IN DISCRIMINATING MEMORY ABILITY OF PSYCHOTICS AND OF NORMALS

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A SLOWLY rotating Archimedes spiral appears to expand or contract, depending upon the direction of rotation. The opposite movement (negative after-effect) is experienced when the rotating spiral is stopped and the gaze is transferred to any other fixed object. Freeman and Josey [1] reported on this phenomenon as a possible measurement of memory impairment. They based their study upon the assumption that normal subjects would experience the negative after-effect while psychotic subjects would not, and would not to the degree that their memory was impaired. Their criterion of memory impairment was clinical judgment. No statistical treatment was given the data, but the authors concluded that there was a "strong probability of correlation between the negative after-effect of the Plateau [Archimedes] spiral and the impairment of memory."

## PROBLEM

The advantage of such a simply administered, nonverbal test of memory impairment is obvious. The present experiment was designed to test Freeman and Josey's "probability of correlation" between the negative after-effect and the degree of memory impairment by using a more objective criterion of memory impairment, the Wechsler Memory Scale.[2]

## METHOD

*Apparatus.*—The negative after-effect phenomenon was generated by using two spiral discs. The spiral on Disc A developed from center to periphery; the spiral on Disc B developed from periphery to center. (One disc would produce both the expanding and the contracting phenomenon if a reversible motor were available.) Both discs were 7 in. (17.8 cm.) in diameter. The spirals were black on a white background, the width of the spiral and the space between spirals being equal—0.4 in. (10.2 mm.). Each spiral developed through 1,305 degrees, i. e., made three and five-eighths revolutions on the disc. The discs were rotated on a standard color wheel, a Variac being used to reduce the current for the required slow rotation.

The subject's experience of the phenomenon was tested by looking at a black spot 7 in. in diameter, mounted on white cardboard 8½ by 8½ in. (21.5 by 21.5 cm.).

Memory impairment was measured by the Wechsler Memory Scale.

*Subjects.*—The "psychotic" group consisted of 25 patients in a state mental hospital. Their diagnoses were as follows: schizophrenia, undifferentiated type, six; schizophrenia, paranoid type, one; schizophrenia, catatonic type, one; manic-depressive psychosis, four; psychosis with mental deficiency, three; dementia paralytica, two; epileptic equivalent, one; paranoid condition, one. Six patients had received no formal diagnosis at the time of testing.

The "normal" group consisted of 16 people with the following backgrounds: janitor, 1; junior high school student, 1; high school student, 1; university students, 7; housewives, 3; nurses, 2, and engineer, 1.

*Procedure.*—All subjects were tested with both discs—half being presented Disc A first, half Disc B first—and with the Wechsler Memory Scale.

The psychotic group were instructed as follows: "I want you to look at two things. First I want you to look at this [pointing to the disc to be set in rotation]; then I want you to look at something else [pointing to the black spot]. Now, when you look at this [pointing to the black spot], something may seem to happen. It may seem to change. You tell me if anything seems to happen." The patient was given no indication that the change would be in size, that the spot would appear to grow larger or smaller, depending upon which disc he had been fixating.

The disc was set in rotation and the examiner instructed the patient to keep looking at the center (pointing to the center). The examiner kept urging the patient to keep looking at the center, to "look real hard just a little longer." After 30 seconds the disc was stopped and the patient instructed, "Now look at this [black spot]. Does anything seem to be happening to it?"

The examiner stood by the rotating spiral to watch the patient's eyes. If the patient was unable or unwilling to fixate for the required 30 seconds, he was excluded from the experiment. Five patients were excluded for this reason.

Instructions for the normal group were simplified to, "Look at the center [pointing to the rotating spiral]. Now look at this [pointing to the black spot] and tell me what happens."

*Distribution of Memory Quotients of Twenty-Five "Psychotics" and Sixteen "Normals"*

| Memory Quotient | Frequency | |
|---|---|---|
| | Psychotic | Normal |
| 49 or lower | 3 | .. |
| 50-59 | 5 | .. |
| 60-69 | 5 | .. |
| 70-79 | 5 | .. |
| 80-89 | 3 | 1 |
| 90-99 | 4 | 1 |
| 100-109 | 1 | 1 |
| 110-119 | .. | 4 |
| 120-129 | .. | 5 |
| 130-139 | .. | 2 |
| 140 or higher | .. | 2 |
| Average MQ | 71 | 120 |

The instructions for administering and scoring the Wechsler Memory Scale were followed verbatim for both groups.

## RESULTS

All subjects, psychotic and normal, experienced the negative after-effect for both discs. The Wechsler Memory Scale scores were transformed into Memory Quotients (MQ) and are presented in the Table. The psychotic group averaged 71 MQ points; the normal group averaged 120 MQ points.

## COMMENT

The present experiment fails to confirm Freeman and Josey's "strong probability of correlation" between the visual phenomenon and the degree of memory impairment. The maximum possible range of MQ points as calculated by the Wechsler Memory Scale is from 48 to 143. The subjects tested in this experiment achieved MQ's fairly evenly distributed through this entire range of possible MQ points (Table). On the visual test, however, all of the subjects experienced the negative after-effect for both the expanding and the contracting phenomenon. In other words, memory impairment to the extent of 48 MQ points on the Wechsler Memory Scale does not prevent a person from experiencing the visual phenomenon. Thus, within the limits of measurement on the Wechsler Memory

Scale, it must be concluded that there is no relationship between the negative after-effect following fixation upon a slowly rotating Archimedes spiral and the degree of memory impairment.

## SUMMARY AND CONCLUSIONS

To investigate the possibility of correlation between ability to perceive a negative after-effect following fixation upon a slowly rotating Archimedes spiral and memory ability (suggested in an article by Freeman and Josey), 25 "psychotic" and 16 "normal" subjects were tested on the visual phenomenon and the Wechsler Memory Scale.

All of the normal group and all of the psychotic group obtained perfect scores in reporting the visual phenomenon. The Wechsler Memory Quotients, however, covered the entire possible range, 48 to 143.

It is concluded that there is no relationship between memory ability and ability to perceive the Archimedes negative after-effect.

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# Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

## Diseases of the Brain

EPILEPSY IN SYSTEMIC LUPUS ERYTHEMATOSUS: EFFECT OF CORTISONE AND ACTH. P. W. RUSSELL, J. R. HASERICK, and E. M. ZUCKER, A. M. A. Arch. Int. Med. **88**:78 (July) 1951.

The discovery of the L.E. (lupus erythematosus) phenomenon in vivo and in vitro has provided accurate diagnostic procedures for acute disseminated lupus erythematosus. These tests have indicated that the disease may exist for varying lengths of time in a previously unrecognized form before entering into the final, familiar clinical picture. This study was prompted by the observation of protracted grand mal attacks in lupus patients with positive reactions to the L.E. test. It is the authors' contention that any patient with epilepsy and rheumatoid arthritis may have systemic lupus erythematosus.

Epilepsy has been the most important, and by far the most frequent, manifestation referable to the central nervous system in patients with proved systemic lupus erythematosus. In this series, 7 of 28 patients with positive plasma L.E. reactions had convulsions during the course of the disease. The incidence of this symptom is significantly greater in this series than among cases accumulated from the literature prior to the introduction of the plasma L.E. test.

Two patients had convulsions for years prior to the appearance of recognizable symptoms of lupus erythematosus. This suggests that epilepsy, when accompanied with rheumatoid arthritis or leucopenia, may constitute a prodromal symptom of systemic lupus erythematosus.

Electroencephalograms frequently demonstrate an organic type of dysrhythmia in patients with or without convulsions associated with systemic lupus erythematosus. Progressive and regressive changes in the electroencephalogram may parallel relapses or remissions in this disease. Routine pathologic studies have failed to reveal specific alterations in the brain in lupus erythematosus.

The authors found that treatment with cortisone and corticotropin produced improvement in epileptiform seizures related to lupus erythematosus. However, the alterations produced in the electrical activity of the brain in cases of rheumatoid arthritis under cortisone or corticotropin administration were not encountered in their patients with systemic lupus erythematosus, six of whom had electroencephalography concurrently with cortisone or corticotropin therapy.

ALPERS, Philadelphia.

RELATION OF CARDIOVASCULAR DISEASE TO APOPLEXY: REVIEW OF 155 CASES WITH AUTOPSY. S. P. HICKS and B. K. BLACK, Am. Heart J. **38**:528 (Oct.) 1949.

Hicks and Black studied the role of systemic circulatory failure in the production of apoplexy in 155 cases of cerebral vascular accident, confirmed by necropsy, in 99 men and 56 women. The apoplexy in all instances was the cause of death or a major factor in bringing it about. Of this series, 118 patients had cerebral hemorrhage; 12 had infarction with thrombosis; 11 had infarction without thrombosis, and 14 had a ruptured aneurysm. Hypertension was present in nearly 90% of the patients. Functional cerebrovascular disease, probably a spasm, appeared to be the important factor in most cases, while systemic circulatory failure accounted directly for few cerebral accidents. The idea of a cause-and-effect relation was entertained in patients with cerebral aneurysm with hypertension.

J. A. M. A.

HEMIPLEGIA ATTENDING ACUTE MYOCARDIAL INFARCTION. W. B. BEAN, G. W. FLAMM, and A. SAPADIN, Am. J. Med. **7**:765 (Dec.) 1949.

Bean and his associates say that it is usually taken for granted that hemiplegia occurring at the time of acute myocardial infarction or shortly after is embolic in origin, the embolus coming from a ventricular mural thrombus. In a survey of a large series of cases of myocardial infarc-

tion verified at autopsy, it was noted that in the majority of cases the hemiplegia which followed infarction of the heart was associated with cerebral arteriosis and local thrombosis, or even hemorrhage, rather than with emboli. The authors made electrocardiograms on many patients with hemiplegia. In several patients the medical history revealed that hemiplegia had appeared shortly after cardiac infarction. The protocols of all autopsies done in the department of pathology of the University of Cincinnati and the Cincinnati General Hospital for the years 1941 through 1946 were investigated for cases in which hemiplegia was precipitated by acute myocardial infarction. The following criteria were used in selection: presence of a gross recent infarct of the heart measuring at least 3 by 3 cm. and of focal neurologic signs suggesting cerebral hemorrhage, thrombosis, or embolism, but absence of evidence of an acute vascular lesion of the cerebral vessels. The authors present clinical and morphologic observations on six patients with major symptoms of acute cerebral disturbance associated with recent infarction of the heart. In all but two patients a myocardial infarct was suspected clinically. There was suggestive evidence that the pattern of local arterial disease in the brain determined the clinical signs and symptoms. A reduction of cardiac output following infarction of the heart may thus lead to the clinical masquerade of an acute cerebral vascular accident. If the hypodynamic state is severe enough, or lasts long enough, vasoparesis, vasoparalysis, and coalescing small hemorrhages may occur. The syndrome has received little attention. If the condition is properly identified and treated, there is some chance that one form of "stroke" will warrant a more optimistic outlook.

J. A. M. A.

CEREBRAL APOPLEXY DUE TO SPONTANEOUS INTRACRANIAL HEMORRHAGE. M. SCOTT, J. A. M. A. **149**:129 (May 10) 1952.

Scott reports 23 cases of surgically treated spontaneous nontraumatic intracranial hemorrhage. The hemorrhage occurred into various lobes of the brain in 20 cases and into the subdural space in 3. The hemorrhages occurred in the internal capsule in nine cases. The youngest patient was 25 and the oldest 70, 75% of the patients being between 40 and 66 years of age. Fifty-two per cent had a history of hypertension before onset of the cerebral accident. Headache occurred in 78%. It always corresponded to the side of cerebral hemorrhage when unilateral. Nuchal rigidity was present in 50%. Only 3 patients were alert on admission; 11 were drowsy, and 9 were in stupor or coma. All patients had neurological signs that permitted accurate localization in the involved cerebral hemisphere.

The spinal fluid pressure was above normal in 90% of the patients; the fluid was blood-tinged or red in 73%. In all the eight patients in whom the pineal gland was visualized by roentgenograms it was found to be displaced, permitting a definite diagnosis of the presence and location of a space-taking clot. Air studies or angiograms were unnecessary for localization in this series.

An exploratory craniotomy was done on 14 patients, and a large trephine opening was made in 9. Liquid clot was found in 4 patients; solid clot, in the remaining 19. Biopsy of the hematoma and the cavity wall or membrane was made in 22 of the 23 cases. An aneurysm was found in 1 patient; rupture of an artery with no visible aneurysm, in 3; brain tumor, in 2, and no obvious cause of hemorrhage in the remaining 17. Eight patients died in the hospital after operation (mortality, 35%, or 28% if the two with brain tumor are excluded). Fifteen patients recovered from the acute episode and were discharged from the hospital.

Scott points out that any person, regardless of age, experiencing sudden headache associated with focal signs, such as aphasia, visual field defect, anesthesia, or hemiplegia, and progressive drowsiness or stupor should be considered to have a space-taking lesion, possibly intracerebral hematoma. In the majority of cases of intracerebral hematoma spinal fluid is bloody and under increased pressure.

Cerebral angiography is not essential as a routine procedure, and its use is not without risk. Although occasionally a patient with intracerebral hemorrhage recovers spontaneously, the majority show progression in focal signs and increased intracranial pressure. The author advocates surgical intervention in this group as a life-saving measure.

ALPERS, Philadelphia.

CEREBELLAR ASTROCYTOMA. N. RINGERTZ and H. NORDENSTAM, J. Neuropath. & Exper. Neurol. **10**:343, 1951.

Ringertz and Nordenstam report on the pathologic anatomy and the biologic properties of the so-called cerebellar astrocytoma, on the basis of a study of 140 patients who were observed and treated over the 25-year period preceding 1948.

In the authors' opinion, cerebellar astrocytoma is a true neoplasm, and not a malformation. The main tumor tissue contains predominantly unipolar and bipolar spongioblasts; and astrocytes, though present, are in the minority. Hence this tumor should be classed as a polar spongioblastoma, not as an astrocytoma. This tumor is very apt to undergo degenerative tissue change, giving rise to an edematous microcystic tissue simulating that of protoplasmatic astrocytoma. Other structural characteristics of the tumor, such as the macrocysts, the peculiar vascular arrangement, and the frequent occurrence of the so-called Rosenthal fibers, are due to the degenerative changes. The tumor frequently infiltrates the neighboring leptomeninges. The adjacent cerebellar gyri present structural changes, caused by pressure and sometimes by tumorous reinfiltration from the meninges.

A small number of the cerebellar tumors in this series were not degeneratively transformed polar spongioblastomas, but true astrocytomas. Also, among the polar spongioblastomas in the central portion of the brain and the brain stem, are tumors with the same structural peculiarities, based on degenerative changes, as those seen in the cerebellar tumors. The frequency of the "cerebellar" type increases as the site approaches the infratentorial region.

Ten cases of cystic polar spongioblastoma located in the cerebral hemispheres are recorded. They presented the same microscopic structure as the cerebellar tumors.

The figures illustrating the biologic properties of the "cerebellar astrocytomas" in this series, such as frequency, sex and age distribution, and duration of the preoperative and postoperative course, correspond well to what has been presented by previous authors. Thus, the postoperative survival rate was encouraging, even of patients with only partially extirpated tumors. However, there was clear evidence in such cases of progressive growth, though this was slow. After radical extirpation, there was only one case of recurrence, and this was the one instance in this series in which the tumor showed transition into malignancy.

The cystic gliomas in the cerebral hemispheres with the same structural type as the cerebellar "astrocytoma" showed a strikingly higher survival rate than the ordinary hemispheric astrocytomas, all of the 10 patients being comfortable as long as 17 years after operation. These cerebral gliomas seem to correspond not only structurally but biologically to the cerebellar tumors.

ALPERS, Philadelphia.

PTERIONAL MENINGIOMAS "EN PLAQUE." F. CASTELANO, B. GUIDETTI, and H. OLIVECRONA, J. Neurosurg. **9**:188 (March) 1952.

The authors report 15 surgically verified and 10 clinically verified cases of sphenoidal meningioma *en plaque*. In 24 of the 25 cases x-ray studies made it possible to verify the diagnosis of sphenoidal meningioma *en plaque*, and even in the remaining case, in which no pathologic changes were reported at the time of examination, a review of the films showed that typical alterations were present.

A diagnosis of pterional meningioma *en plaque* is supported by the following factors: (1) occurrence usually in a woman of middle age; (2) history of slowly developing exophthalmos, with ultimate impairment of vision on the affected side; (3) temporal swelling, and (4) x-ray findings of hyperostosis involving the sphenoidal ridge, the greater and lesser wing of the sphenoid bone, and the root of the orbit. Exophthalmos is the most important symptom. It is unilateral, nonpulsating, and irreducible, and the eyeball is displaced forward and downward.

In the cases of meningioma in which operation was not done the encephalograms showed little or no ventricular displacement, or only a slight dislocation. In the verified cases the alterations were displacement, varying from 1 to 10 mm., of the anterior part of the ventricular system toward the normal side and displacement of the tip of the temporal horn backward, upward, and medially.

Two of the 15 on whom operation was performed were operative fatalities. Of the 13 patients who survived operation, 1 died after 35 days of pulmonary abscess; 7 were well or had only

defects that did not seriously affect their earning capacity, and 5 were unimproved or in worse condition than before operation. The exophthalmos of six patients was improved after operation. Of two patients on whom operation was performed for recurrence two years after the first operation, one survived seven years, and the other, two years. Two patients died after about two years, from probable continuation of the growth.

The 10 patients who, because of slight clinical discomforts and little or no ventricular displacement, did not have surgical treatment were under observation for 13 years. Examination of these patients has shown that, except for two who died of intercurrent disease, they are well and active.

The results of this investigation would seem to indicate that the hyperostosing meningiomas of the greater and lesser wings of the sphenoid bone that cause only slight subjective complaints and with which no marked displacement of the ventricles can be found should, as a rule, not be operated upon and that surgical measures should be considered only as a last resort.

ALPERS, Philadelphia.

TUMORS OF THE GASSERIAN GANGLION. H. M. CUNEO and C. W. RAND, J. Neurosurg. **9**:423 (Sept.) 1952.

Cuneo and Rand review the literature of tumors of the Gasserian ganglion and report an unusual case of tumor involving the Gasserian ganglion and the mandibular and maxillary divisions of the trigeminal nerve.

The patient, a man of 37, had suffered from a burning numbness, which gradually became painful, on the left side of his lower lip and chin for two years. Recently the pain had involved the left side of his tongue and of his face. On examination the cranial nerves appeared entirely normal, with the exception of the left fifth. There was slight numbness of the left side of the lower lip in the region supplied by the mental branch of the mandibular nerve. There seemed to be slight numbness of the tragus of the left ear. The corneal reflexes were active and equal, and there was no anesthesia of the cornea. The motor component of both fifth nerves was intact, and no evidence of wasting of the muscles of mastication was present. Both seventh nerves were normal. There were no other neurological abnormalities.

Roentgenograms of the lower jaw were taken and repeated after an interval of three months. During this time there was an extraordinary enlargement of the inferior dental canal and mental foramen on the left side. The possibility of a tumor was raised.

Exploration of the ganglion was done months later. A biopsy of the mental nerve was reported as showing "marked inflammatory change and fibrosis—etiology not apparent."

The patient noted discomfort and numbness creeping up the left side of his cheek in the months following. His face was definitely swollen on the left. He showed some involvement of the left mandibular and maxillary divisions, but none of the ophthalmic division. An x-ray taken four months later showed that the foramen ovale on the left side had continued to increase in size, being now approximately three times the average size. One month later operation was performed and a tumor of the Gasserian ganglion was removed. The diagnosis of probable malignant schwannoma was made by one pathologist; that of an unclassified tumor resembling a neurofibroma, by another. From the appearance of the enlarged mandibular canal, without further invasion of the mandible, it would appear that this lesion was a rapidly growing primary tumor of the mandibular nerve, a malignant schwannoma, which involved the Gasserian ganglion.

ALPERS, Philadelphia.

THE ELECTROENCEPHALOGRAM IN SUBDURAL HEMATOMA. L. L. LEVY, L. H. SEGERBERG, R. P. SCHMIDT, R. C. TURRELL, and E. ROSEMAN, J. Neurosurg. **9**:588 (Nov.) 1952.

In this study, the electroencephalographic findings for 60 patients with severe head injuries were reviewed. Attempts were made to establish the diagnosis of subdural hematoma on the basis of the initial records. Serial records were examined for additional diagnostic clues. In all instances there were an initial period of coma following the injury, bloody cerebrospinal fluid, a subsequent period of mental depression, and/or increasing abnormal focal neurologic signs. By such clinical criteria, any of these 60 patients could have been suspected of having either unilateral or bilateral subdural hematoma.

Thirty of the patients had proved subdural hematomas. Of the other 30, 16 had no evidence of hematoma on bilateral exploration; 3 showed no evidence of hematoma at autopsy; 11, of whom 5 had normal pneumoencephalograms, returned to normalcy clinically. No data are presented on bilateral subdural hematoma or the electroencephalographic picture in infants.

The findings in this survey indicate that the initial electroencephalogram is identical in these two groups of head injuries, i. e., those with and those without subdural hematoma, and hence their differentiation is impossible on this basis. The parameters of ipsilateral reduction in amplitude and slow-wave focus are similarly present in both regardless of whether the initial electroencephalogram is taken in the acute, the subacute, or the chronic stage. Hence, with one possible exception, noted below, it would seem that the initial electroencephalogram is of no value in the differentiation of the "operative" and the "nonoperative" type of head injuries, particularly as concerns unilateral subdural hematomas in adults.

Five cases of subdural hematoma with ipsilateral paralysis are presented. In all these instances the hematoma was present on the side of the reduction in amplitude and the slow-wave focus.

ALPERS, Philadelphia.

BILATERAL NASOETHMOIDAL ENCEPHALOCELE. A. MARSCHAK and G. RIESENFELD, Harefuah **45**:224 (May 15) 1953.

Marschak and Riesenfeld report a case of nasoethmoidal encephalocele in a Yemenite infant. Of 106 cases in the literature, there were only 2 in which the encephalocele was bilateral. An 8-day old Yemenite infant had bilateral swelling of the face between the nose and the eye; the swellings were tense and bluish-red and failed to transilluminate properly. A roentgenogram of the skull showed a defect in the bone between the frontal and the nasal bones on the left; the sutures of the skull were not widened. No abnormality of the child's general condition was found, and no other defects were noted. Some of the swelling from each side of the naso-ocular region was removed, without complete disappearance of the deformities. Four weeks after the operation, at the age of 24 days, the child died. Autopsy revealed that the lamina cribrosa was absent bilaterally, and the right frontal lobe extended toward the left side through a defect in the falx membrane. The authors suggest an intracranial approach in cases of this type in the future.

N. SAVITSKY, New York.

NEUROSURGICAL TREATMENT OF HEREDITARY OPTIC ATROPHY. H. VERBIEST, Rev. neurol. **80**:657 (Nov.) 1948.

Verbiest does not distinguish between classic Leber's optic atrophy and subtypes. Reviewing the meager pathologic knowledge to date, he points out that coexistent with the early clinical phase of hyperemia and swelling of the disk are hyperemia of pial vessels and perivascular infiltrations of lymphocytes. Previous reports of surgical intervention have frequently stressed the presence of optochiasmic arachnoiditis. However, in many cases this condition is not sufficient to explain the pronounced clinical signs.

Verbiest operated in 11 cases. In seven there was marked adhesive arachnoiditis surrounding the optic nerve; in 2, slight, and in 2, none. No relation could be found between the severity of the lesions and difficulties in vision. For this reason, the author does not feel that stripping of arachnoidal adhesions is desirable.

Only two patients failed to show improvement during a follow-up period of five years. Comparison of the general vision of these operative patients with that in a large series of Lundsgaard's showed that only one of the author's patients had vision as poor as 84% of Lundsgaard's series. Verbiest notes the benefit occasionally derived from nonspecific operations. He notes Puech's unusual experience of improvement in a case of arachnoiditis of the optic nerve following a trephine opening alone. In one of the author's cases improvement followed a simple exploration of the area of the optic chiasm. He notes improvement reported from operation on the sinuses, particularly the ethmoid cells. Carotid sympathectomy has also been reported favorably, as has the use of acetylcholine and nicotinic acid. The author, therefore, states that the vasodilatory action of the operation is the probable beneficial factor. He believes that the mechanism underlying the disease is an acute angiospastic neuropathy, probably due to reflex angiospasm of vessels implicated in the arachnoiditis. In one of his cases injection of atropine into the area of operation caused complete disappearance of a central scotoma for several hours.

The author concludes: "We believe that in Leber's disease, besides the hereditary degenerative predisposition of the optic fibers, there is a vascular factor which can cause abrupt onset of the sickness or aggravate or maintain it. In our opinion, optochiasmic arachnoiditis plays a role in the pathogenic mechanism. Extirpation of arachnoidal adhesions can produce a reactive hyperemia in the optochiasmic system, resulting in considerable visual amelioration." The hyperemia, in the author's opinion, is caused by partial adventitial stripping of the vessels of the area, which, in effect, is a regional sympathectomy.

LEGAULT, Washington, D.C.

COCHLEAR AND VESTIBULAR SYMPTOMOLOGY OF ACOUSTIC NEUROMA. H. GIROIRE, A. CHARBONNEL, and J. COLAS, Rev. oto-neuro-opht. **21**:306 (July) 1952.

The authors report the cochlear and vestibular changes in eight verified cases of acoustic neuroma. In all cases there was deafness on the side of the tumor and a complaint of unsteadiness. Deafness in all cases was of long duration—2 to 12 years. The unsteadiness in all the cases was more recent—a few weeks to a few months. Tinnitus was noted only in two cases; in one it was bilateral and was present for only a few weeks in a patient who had been deaf for 12 years. Dizziness, which was recent in all cases, was reported in four cases. True vertigo, during which external objects rotated about the patient, was not present. Dizziness was mainly in the nature of unsteadiness with change of position, sometimes accompanied by sudden weakness of the lower limb. There was a long first stage, of many years' duration, in which the only complaint was unilateral deafness, with no dizziness or buzzing in the ears. The second stage was of more recent onset and shorter duration. Unsteadiness was in the foreground of the clinical picture.

The deafness on the side of the tumor was complete in seven of the eight cases. That the impairment was of the inner ear type in all cases was readily demonstrable by the Weber and Rinne test and confirmed by audiometric investigation. Nystagmus was present in seven cases and was always bilateral, being occasionally more pronounced in one direction. In four cases it was horizontal, and in three, rotatory. In two of the three cases the nystagmus was horizontal in one direction and rotatory in the opposite direction. In one case the unsteadiness was so great that the Romberg sign could not be tested for. In some cases, in spite of unsteadiness of gait, there was no swaying during the Romberg test. In six cases there was some veering toward one side, sometimes with some degree of retropulsion. Deviation of the outstretched upper limbs was found five times. The authors also note that the vestibular syndrome was usually incomplete. In the second case there was no deviation of the outstretched upper limbs; in the third there was no veering in spite of definite nystagmus, and in the fifth there was no nystagmus but definite veering occurred. In the sixth case there was no deviation of the outstretched upper limbs in spite of bilateral nystagmus and severe unsteadiness. In the first case there was also a so-called disharmonious vestibular syndrome—deviation toward the left in the Romberg test and deviation of the right upper limb. These findings point to a probable central origin for the vestibular disturbances.

In each case there was impairment of the caloric response on the involved side; in two cases this caloric inexcitability was incomplete.

All the tumors removed were relatively large, being about the size of a pigeon egg. They all extended beyond the internal auditory meatus and compressed the brain stem. The deafness and caloric inexcitability are manifestations of peripheral compression of the eighth nerve, and the central vestibular syndrome is due to impingement on the brain stem.

N. SAVITSKY, New York.

ALTERNATING OPTICOPYRAMIDAL HEMIPLEGIA. MANCEAUX, JORDA, and TIMSIT, Rev. oto-neuro-opht. **24**:461 (Nov.-Dec.) 1952.

The only similar cases the authors cite are those of Radovici and Lasco, who in 1948 reported four cases with pyramidal tract signs on one side of the body and contralateral optic nerve atrophy. They report the case of a woman aged 53 who was hospitalized with left hemiparesis. The onset of the illness occurred 18 months previously with paresthesias and heaviness in the left lower extremity; later the left upper limb became involved. Six months later, or a year before

admission, weakness suddenly developed on the left side of the body. At the same time diminished vision was noted in the right eye; in three months there was no sight in that eye. During the year before admission the hemiparesis gradually improved. Examination showed spastic left hemiparesis, with greater involvement of the upper limb and face; there was no Babinski sign; there was hyperreflexia on the left side; a Rossolimo sign and a Hoffmann sign were elicited on the left side; the abdominal reflexes were absent bilaterally; there were no sensory changes. Ophthalmological examination showed absence of direct response to light in the right eye, with intactness of the consensual reflex and of pupillary reactions in accommodation, and primary optic atrophy with thin arteries. There was evidence of a chronic pulmonary infection, with two areas of infiltration and accentuation of pulmonary markings. There was definite arteriosclerosis, and the second heart sound was accentuated. The blood pressure was 130/80. The blood Wassermann reaction was negative, and the blood chemistry was normal. The electroencephalogram showed a focus of slow waves in the middle of the right hemisphere, suggesting a focal lesion. Right-sided angiography showed marked changes in the region of the carotid artery, which was very thin, especially terminally; the carotid siphon was also very thin and irregular. A positive de Milletti sign was noted (syncope on compression of the contralateral intact left carotid artery). The carotid pulses were palpable and equal bilaterally, indicating that the lesion was probably in the terminal portion of the right internal carotid artery. The intermittent course is emphasized; the carotid thrombosis probably did not cause complete occlusion.

N. Savitsky, New York.

Foster Kennedy Syndrome and Hydrocephalus. Giroire, Legrand, Charbonnel, Colas, and Vercelletto, Rev. oto-neuro-opht. **25**:96 (Feb.-March) 1953.

A girl aged 19 was first seen because of diminution of vision and headache. The precise duration of the complaints was not determined. Ophthalmologic examination showed primary optic nerve atrophy on the left side, with incorrectible diminution of vision and a central scotoma. There was papilledema in the right eye, with no striking diminution of vision. The neurologic examination was noncontributory. Roentgenograms of the skull showed increased digitations, pointing to long-standing increased intracranial pressure. An operation was suggested because of the possibility of chiasmal arachnoiditis secondary to meningoencephalitis in early childhood; the patient refused to undergo operation.

She was seen again almost five years later, in the fifth or sixth month of pregnancy, because of headache, somnolence, and diminution of vision, as well as pain in the right side of the face. Neurologic examination showed a Foster Kennedy syndrome, as previously noted, with greater diminution of vision, drift of the right upper limb, and mild hyperpronation of the right hand. An electroencephalogram showed a focus in the left frontoparietal region. An x-ray of the skull showed no changes in the sella or the sphenoidal ridges; the increased digitations of the skull were practically unchanged. Birth was induced. At a left frontoparietal operation soon afterward no tumor was found; the third ventricle, which was greatly dilated, was punctured; the left lateral ventricle was also dilated. The optic nerves appeared similar. After the operation, vision in the right eye improved slightly; the headaches, drowsiness, and changes in the right upper limb disappeared. The electroencephalographic changes in the left hemisphere became less pronounced. Hydrocephalus may be the cause of a Foster Kennedy syndrome. It is difficult to explain the clinical changes by a marked dilatation of the third ventricle, which more frequently causes a chiasmal syndrome with a bitemporal field defect. The authors suggest that compression of blood vessels supplying one of the optic nerves accounts for the difference between the two eyes.

N. Savitsky, New York.

Fatal Toxic Encephalitis Due to Streptomycin. D. Campanacci, Minerva med. **40**:751 (Nov. 24) 1949.

Campanacci reports on a 35-year-old woman who was receiving intramuscular injections of streptomycin for the treatment of pleurisy. She received 1 gm. of the drug daily in three fractional doses for nine consecutive days. Symptoms of acute encephalitis appeared on the 10th day, one hour after administration of the first dose. The patient died three days later. This is the second case of fatal encephalitis caused by streptomycin observed by the author. Both patients

complained three or four days before the appearance of encephalitis of nausea, vomiting, dizziness, noises, fatigue, and depression. The neurotropic effects of the drug are particularly likely to manifest themselves in persons with renal or hepatic insufficiency and in patients who had received penicillin or sulfanilamide a few weeks before the administration of streptomycin. The appearance of mild toxic symptoms, which indicate nervous intoxication, is an indication for discontinuation of streptomycin and immediate administration of dextrose in large doses, of vitamin B and ascorbic acid, and of cardiac tonics. Streptomycin therapy in the course of penicillin or sulfanilamide therapy is not desirable except when the combination of the two is definitely indicated.

J. A. M. A.

BILATERAL MALIGNANT EXOPHTHALMOS AND ENLARGEMENT OF BOTH INTERNAL CAROTID ARTERIES WITH PERICAROTID NEURITIS. G. CRISTINI, Riv. oto-neuro-oftal. **24**:232 (May-June) 1949.

A laborer aged 68 was hit in the head with an iron beam and was unconscious for a short time. He got up by himself and went to a hospital, where he was treated for a scalp wound. Soon after this accident he began to complain of recurring pain in the head at the site of the injury, ringing in the ears, and dizziness, especially when he bent his head forward. After about a year he began to have occasional attacks of mild hemicrania with discomfort in the region of the right eye. During November, 1946, the discomfort in the right eye became worse, especially when he bent his head forward; he began to hear a mild bruit, and prominence of the right eye also appeared. The condition became worse when he bent his head forward or when he blew his nose or sneezed. A diagnosis of orbital varices was made in a hospital, and sclerosing fluid was injected into the orbit. After this procedure, the exophthalmos became worse; chemosis appeared, and a tarsorrhaphy had to be done to prevent corneal ulceration. Exploration of the orbit was done through the transconjunctival route, but nothing but edema was found in the retrobulbar region. Soon afterward "malignant" exophthalmos appeared in the left eye, with bruit on that side. He was admitted to the hospital, where the metabolic rate was found to be —28%; six days later it was —5%. Marked exophthalmos was found in the left eye, with edema, chemosis of the left lower lid, and corneal ulceration. There was paralysis of upward and downward gaze, but lateral movements were intact. In the right eye, the lids were almost completely sewn together; the cornea was infiltrated, and the eyeball seemed prominent. There was marked diminution of sensation in the first division of both fifth nerves. Attacks of disorientation and inability to pay attention were also noted. Carotid arteriography was performed first on the right and then on the left side, the arteriograms showing large cartoid arteries and dilatation of the ophthalmic and orbital vessels. The sphenopalatine ganglion was injected bilaterally with 5 cc. of 45% ethyl alcohol and 1 cc. of 2% procaine hydrochloride. Four days later there was less retrobulbar discomfort and a bruit was no longer heard. Exophthalmos remained the same, but chemosis was somewhat less. Later, the exophthalmos was definitely less bilaterally, and the chemosis on the left side had disappeared. There was a large scar on the left cornea with impairment of vision. His condition was unchanged three months later. Biopsy of the conjunctival tissue of the left eye showed edema and dilatation of blood vessels; the vessels were filled with red cells, and there was perivascular cuffing with red cells.

The malignant exophthalmos is considered to have been a sequel of the trauma to the head in 1940. The retro-orbital edema was due to long-standing dilatation of the small vessels of the orbit, resulting from a post-traumatic cerebral vasomotor disorder. Some of the pain about the face and the hemicrania during the first year after the accident was due perhaps to pressure on the sympathetic fibers running along the carotid artery. The author admits that hyperthyroidism may play an etiologic role in accounting for this syndrome.

N. SAVITSKY, New York.

SUPRANUCLEAR OCULAR PARALYSIS DUE TO QUININE POISONING. V. CIMA, Riv. oto-neuro-oftal. **27**:227 (May-June) 1952.

Cima reports a case of supranuclear ocular paralysis due to quinine toxicity. No similar case was found in the literature. A woman aged 29 was admitted because of a suicidal attempt by the ingestion of a large amount of quinine. At the age of 17 she was admitted to a psychiatric

hospital, from which she was discharged in a few months after narcoanalysis and a course of insulin coma treatment. An ocular examination one and a half years before the suicidal attempt showed some ptosis on the right and readily correctible myopia in both eyes. There was no evidence of external or internal ophthalmoplegia.

She was seen by an ophthalmologist seven days after the suicidal attempt. He found marked diminution of visual acuity in both eyes, with only light perception. There were pronounced atrophy of the disks and slight edema around them. Movements of the eyeballs were not possible; there was normal reaction of the pupils to light but not during convergence. Two months later reexamination showed bilateral hippus. The pupils reacted normally to light, with intact consensual responses. The patient was unable to converge the eyes. There was no spontaneous nystagmus. Mild ptosis was present on the right, with complete paralysis of gaze in all directions. Neurologic examination showed steppage gait in the left lower limb, with a tendency to foot drop; mild myoclonic twitches in the lower limbs, especially on the left side, and some tenderness at the site of emergence of the second and third divisions of the fifth cranial nerve bilaterally. The palate was asymmetrical, with deviation to the left, and the tongue deviated to the left. There was slight weakness in the left lower limb, with a tendency to hyperreflexia; the left abdominal reflexes were diminished. There was fanning of the toes on the left with plantar stimulation. Pneumoencephalography showed slight deviation of the ventricle to the left. The spinal fluid was normal. Vestibular tests gave normal results. Ophthalmologic examination at this time showed atrophic disks with narrowed arteries, brownish discolorations in the macular areas, and in one of the eyes, some pigmentary deposits in the periphery. The visual acuity was limited to light perception with ability to differentiate different light intensities. The visual fields could not be determined. The pupils were in middilatation and reacted restrictedly to light. Convergence was impossible. Voluntary movements of the eyeballs were impossible except for a few jerks on upward gaze suggesting nystagmoid movements. Because of the inability to fixate, it was impossible to test the oculovestibular reflex turning of the eyes with passive movements of the head. Rapid turning of the head caused some reflex conjugate deviation to the opposite side; Bell's phenomenon was present. No movements of the eyeball were noted while the patient was drowsy after the injection of thiopental (Pentothal) sodium.

The absence of voluntary eye movements, the intactness of Bell's phenomenon, and the reflex response of the eyeball to vestibular stimulation indicate a supernuclear ophthalmoplegia. There was in addition some pyramidal tract involvement on the left side.

N. Savitsky, New York.

Multiple Sclerosis-Cervical Cord Syndrome Slowly Progressing over a Period of Sixteen Years. L. Barraquer-Bordas and J. M. Segarra-Oriol, Arq. neuro-psiquiat. **10**:247 (June) 1952.

The authors report an unusual case of multiple sclerosis with anatomical verification in a 42-year-old woman with a history of a progressive lesion of the cervical portion of the cord of 16 years' duration. The onset was in 1935 with weakness of the right lower limb, followed soon by weakness of the left leg. Examination on Oct. 8, 1936, revealed spastic paraparesis with hyperreflexia, a bilateral Babinski sign, and sphincteric disturbance. The Wassermann reactions of the blood and spinal fluid were negative; the colloidal gold curve was not of dementia paralytica type. On June 21, 1950, the patient was admitted to the hospital with a history of progressive weakness and atrophy of the left hand for a few years; weakness of the legs also became increasingly severe. There was no history of remission. Examination in 1950 showed spastic paraplegia with flexion contractures and atrophy of the acral muscles of the upper limbs without fibrillations, especially on the left side. There were hyperreflexia of all tendon reflexes below the sixth cervical segment and diminution of pain and temperature sense up the upper extremities, without a clear-cut upper level. There was no intention tremor or involvement of cranial nerves. There was impairment of vibration and position senses in both lower limbs and in the left hand, and sphincteric difficulties were present. She did not complain of paresthesia in the trunk or limbs. There was some pain in the upper portion of the spine. No manometric

block of the spinal fluid was found; there were 0.2 cell per cubic millimeter and 20 mg. of protein per 100 cc. The Wassermann reaction was negative. An ophthalmoscopic examination during October, 1950, showed a mild degree of optic nerve atrophy. Injection of iodized oil (Lipiodol) showed no block. On Jan. 2, 1951, laminectomy from the second to the seventh cervical vertebra, was done, but no tumor was found; the cord looked pale. The patient died on Jan. 6, of pneumonia. Autopsy showed multiple sclerosis involving the cord and brain. The author emphasizes the presence of disseminated lesions in the nervous system without clinical manifestations.

N. Savitsky, New York.

Cerebral Disease in Relation to Gastric Ulcer. M. Staemmler, Deutsche med. Wchnschr. **74**:1485 (Dec. 9) 1949.

Staemmler investigated the neurologic and neurosurgical necropsy material at his hospital for erosions and ulcerations in stomach and duodenum. Of 36 patients with acute fatal brain lesions (operations on the brain, suppurating meningitis, encephalitis, etc.), 10 had erosions of recent date in the stomach or duodenum. This series does not include observations on the newborn. Of 50 patients with chronic brain lesions (old injuries, abscesses, and tumors), only 1 had a scar in the duodenum; a recent, still active ulcer was never observed. Observations indicate that the gastroduodenal erosions which exist in the presence of severe cerebral lesions are the result of a centrally induced circulatory disturbance, which begins with hyperemia and develops into hemorrhagic infarction. The mucosa thus damaged is eroded by the gastric juice. A causal connection exists between the cerebral lesion and the erosion in stomach or duodenum, which may be limited to the mucosa or may penetrate the entire wall and lead to perforation. In some cases a hemorrhage in the mucosa may be sufficient to reduce resistance to the digestive action of the gastric juice. Such hemorrhages of central origin are known to occur also in the lung and in the mucosa of the bladder. It is difficult to ascertain whether the erosions of central origin may develop into true chronic ulcers. The author believes that this is the exception and that the erosions usually heal when the cerebral irritation subsides. His investigations provided no proof that true chronic gastric or duodenal ulcers developed from the centrally induced erosions.

J. A. M. A.

## Treatment, Neurosurgery

Surgical Management of Shoulder Girdle Syndromes. J. W. Lord Jr., A. M. A. Arch. Surg. **66**:69, 1953.

Signs and symptoms of the various shoulder girdle syndromes are due to pressure, torsion, or traction exerted on the subclavian artery, the subclavian vein, and the brachial plexus. Careful clinical analysis is necessary to evaluate whether the symptoms are due to pressure on the anterior scalene muscle, with or without a cervical rib, to a narrowing of the costoclavicular space, or, finally, to a hyperabduction syndrome. Not only neurologic and roentgenologic studies, but also a detailed investigation of the circulatory state of the upper extremities (by means of oscillometry and angiography), is required. In any given case several syndromes may be operative.

Although conservative treatment relieves satisfactorily the symptoms of many patients, surgical intervention may occasionally become necessary. The author proposes a surgical procedure which attempts to correct all faulty mechanical factors. This operation consists of a total removal of the clavicle, including its periosteum, section of the anterior scalene muscle, and caudad mobilization of the subclavian artery. This operation is indicated in patients with arteriol thrombosis and in those who have not responded to any form of conservative treatment. The procedure described was employed in nine cases, with excellent results in five, good results in three, and a fair result in one. The postoperative disability has been relatively mild and lasts usually less than a month. Before a final evaluation of this procedure can be made, a larger number of patients should be followed over a longer period. Three illustrative case histories are reported in detail.

List, Grand Rapids, Mich.

COMBINED PENICILLIN AND MALARIAL FEVER TREATMENT IN CEREBROVASCULAR SYPHILIS. WALLIS L. CRADDOCK, Dis. Nerv. System **10**:55 (Feb.) 1949.

In his review of the pertinent literature, Craddock finds that most authorities favor combined penicillin and fever therapy in neurosyphilis, rather than treatment with either agent alone. However, there is sufficient evidence at hand to justify the treatment of asymptomatic neurosyphilis with one or several courses of the antibiotic before malaria is resorted to. The case described is that of a 52-year-old man who presented the general picture of severe dementia paralytica, although the onset two weeks before had been of the acute vascular type. Five months previously he had been noticed to have evidences of brain involvement, as indicated by speech difficulties, and at that time had been given 4,000,000 units of penicillin in nine days. After hospitalization, antibiotic therapy was cautiously instituted, and 11,000,000 units was given over a period of 37 days. Because of the prior downhill course, and in spite of the dangers of malaria following a vascular accident, he was inoculated with Plasmodium vivax and had 11 paroxysms and 48 hours of fever at a temperature of over 104 F. before termination of this phase of the treatment, 21 days later. The third part of the regimen was another 11,000,000 units of penicillin in 25 days. The patient has been able to achieve a full "social recovery," and his spinal fluid is normal, after 18 months. It is believed that in any case of this severity intensive combined therapy, with a full course of malaria, is required.

BEATON, Tucson, Ariz.

EVALUATION OF STELLATE GANGLION BLOCK FOR ACUTE FOCAL CEREBRAL INFARCTS. CLARK H. MILLIKAN and LUCIAN A. SMITH, J. A. M. A. **151**:438 (Feb. 7) 1953.

The authors introduce a question concerning the value of stellate ganglion block as a treatment for focal cerebral vascular disease and point out that the literature does not contain enough careful observations concerning this matter to make an answer to the question possible.

Millikan and Smith here describe a method of caring for patients with this disease. This method makes possible ultimate comparison of the results of different types of treatment. This preliminary report is concerned with observation of 87 patients—60 without stellate block and 27 with it.

While this number is insufficient to permit valid statistical analysis of the results, the authors have been unable to confirm the claims of remarkable improvement of patients with focal cerebral vascular disease after stellate ganglion block, as reported by many authors. Thus far the principal difference in their two groups of patients has been in mortality in simple cerebral infarction. This mortality rate was 19% in those having repeated stellate ganglion block and 8% in those not receiving this treatment. Thirteen per cent of the group not receiving blocks were normal two weeks after the occurrence of infarction, as contrasted with 5% of those receiving stellate blocks.

The two groups of patients were comparable from the standpoint of the severity and extent of the lesions. Hemiplegia developed in 55% of the patients receiving stellate ganglion block within 24 hours after the onset of symptoms, and 51% of the nonblocked group developed hemiplegia in the same time period. In most instances the first stellate block for each patient was performed from a few minutes to six hours after the onset of symptoms of infarction. Three patients actually had effective stellate blocks during the onset of the symptoms and still continued showing progressive loss of function until hemiplegia was present.

ALPERS, Philadelphia.

SUCCINATE THERAPY IN MULTIPLE SCLEROSIS. R. B. AIRD, Neurology **1**:219 (May-June) 1951.

Sodium succinate was administered intravenously to 10 patients with multiple sclerosis and orally over prolonged periods to 22 patients with the disease. Subjective improvement was reported in 80%, and objective improvement was observed in approximately two-thirds of the patients with both methods of treatment. More prolonged follow-up observations on patients treated orally with succinate suggested that approximately one-half of them were benefited.

Toxic effects were observed in one patient treated intravenously and in six patients given the drug orally. The toxic effects in the latter were not alarming, and three of the patients

were able to continue the oral treatment in reduced doses. Deterioration of the patient's condition on discontinuation of the succinate was observed in four instances. They all improved on resumption of the treatment. Recurrent episodes were observed in three patients.

Aird discusses the rationale for the use of sodium succinate in multiple sclerosis and considers certain deductions with respect to its physiologic effects in terms of the neuropathology of multiple sclerosis.

ALPERS, Philadelphia.

MESANTOIN IN THE CONTROL OF EPILEPSY. A. E. LOSCALZO, Neurology **2**:403 (Sept.) 1952.

This study reports the effect of methylphenylethyl hydantoin (Mesantoin) therapy in a group of 224 clinic and private patients treated over a period of from one to seven years. Of these patients, 182, or 81%, derived definite benefit. A 50% reduction in expected grand mal seizures was obtained as compared with the results of previous medication.

Sensitive patients can react severely to Mesantoin therapy. For this reason, Loscalzo outlines the following program to keep side-reactions at a minimum. 1. Patients with past histories of allergy or drug sensitivity should be treated with caution. 2. Patients requiring a large dose (0.8 gm. or more) should be watched carefully. 3. The drug must be discontinued immediately if rash, abnormal vaginal bleeding, or bleeding from the gums occurs. 4. A careful investigation of the case should be made and the dose of Mesantoin reduced if pruritis, lacrimation, "canker sores," or postauricular exfoliation occurs.

In this study, 16% of the patients complained of drowsiness, which could be controlled with amphetamine (Benzedrine) when severe; 9% had a rash; 5.5% manifested a mild pancytopenia, not requiring discontinuation of the drug, and one patient had moderate pancytopenia, requiring careful observation.

In this series, of 224 patients, 15 became pregnant and continued taking the drug throughout their pregnancy, without any ill-effects. They were delivered of sound infants, with no side-reactions in either the mothers or the infants.

In this study, Mesantoin has proved to be a most efficient antiepileptic drug. Loscalzo feels it is indicated in cases in which toxic symptoms to diphenylhydantoin, phenobarbital, or other anticonvulsant drugs develop, in cases in which the seizures are not adequately controlled by other drugs, and in all new suitable cases of grand mal epilepsy. A careful therapeutic regimen must be followed in each case, in addition, care must be taken to adjust the dose for each individual patient, so that untoward reactions can be kept to a minimum.

ALPERS, Philadelphia.

EFFECTS OF CORTISONE IN MYOTONIA ATROPHICA. R. W. BARRIS and H. D. STRASSMAN, Neurology **2**:496 (Nov.-Dec.) 1952.

This paper deals with a study of the effect of cortisone in myotonia atrophica, together with a brief summary of the present status of corticotropin and cortisone in treatment of the neuromuscular disorders.

Cortisone acetate was administered orally and intramuscularly to six patients with myotonia atrophica in daily doses of 100 to 250 mg. During cortisone therapy there was noted a reduction in the myotonic contraction of muscles, a decreased 24-hour urinary excretion of 17-ketosteroids, and a fall in urinary creatinine excretion. Prior to, during, and after cortisone therapy, frequent estimates were made of the blood serum levels of sodium, potassium, cholesterol, cholesterol esters, creatine, and glucose. Alterations in the levels of these substances were not significant.

Incidental observations made on the six patients include increased growth of scalp, facial, and body hair and increased sense of well-being.

Cortisone was administered for periods ranging from 15 to 22 days, the average being 21 days, after which it was discontinued. Within 72 hours after discontinuation of the drug, the myotonic reactions, as revealed by thenar percussions, forearm percussion, and opening and closing of the hands, resumed the status observed prior to therapy.

ALPERS, Philadelphia.

DECOMPRESSION OF THE GASSERIAN GANGLION AND ITS POSTERIOR ROOT: A NEW TREATMENT FOR TRIGEMINAL NEURALGIA (PRELIMINARY REPORT). J. G. LOVE, Proc. Staff Meet., Mayo Clin. **27**:257 (July 2) 1952.

Grafton describes a new technique devised by Dr. P. Taarnhöf. This operation consists of decompressing the Gasserian ganglion and its posterior root without dividing any of the sensory fibers of the ganglion. Dr. Taarnhöf had performed this operation in 10 cases of trigeminal neuralgia and relieved all 10 patients without producing any sensory loss in the trigeminal distribution. Dr. Gösta Norlén also had performed 10 such operations, with an equally brilliant result.

Love tried this new operation on a woman suffering from pain in the first and second divisions of the trigeminal nerve on the right side. She twice had been relieved temporarily by injection of alcohol into the involved branches. When the numbness produced by the injections of alcohol disappeared, the pain recurred. The operation was performed, and when the patient was discharged six days after operation, she was free of pain and without loss of sensation in the distribution of the trigeminal nerve.

Taarnhöf and Norlén used a temporal craniectomy such as had been used in the Frazier-Spiller operation, but they approached the sheath of the ganglion and its root transdurally and under the temporal lobe. Love employed an extradural approach to the ganglion, feeling that this approach is safer and less likely to result in complications.

ALPERS, Philadelphia.

THE TREATMENT OF ACUTE ALCOHOLIC STATES WITH ACTH [CORTICOTROPIN] AND ADRENOCORTICAL HORMONES [CORTISONE]. J. J. SMITH, Quart. J. Stud. Alcohol **11**:190 (June) 1950.

Smith reports on the effect of corticotropin (ACTH) and cortisone (adrenocortical hormone) in the treatment of Korsakoff's psychosis, acute alcoholic intoxication, and delirium tremens. The patients received 85 mg. of corticotropin intramuscularly every six hours around the clock. They were not given sedation or supportive therapy. There was pronounced, almost dramatic, improvement within 18 hours in five patients treated with cortisone for Korsakoff's psychosis. Corticotropin had little effect except for some diminution in restless excitement. Both drugs appeared to be almost equally effective in the treatment of acute alcoholic intoxication. Cortisone had a much prompter sedative effect than corticotropin and abolished anorexia more quickly. These results were superior to those obtained in 4,000 alcoholics treated conventionally. Cortisone is probably preferable to corticotropin treatment of acute alcoholic intoxication because of its superior sedative action.

Corticotropin, which was given to six patients with delirium tremens, was dramatically effective and was superior to cortisone, which was given to 40 patients, and to cortisone and desoxycorticosterone, given to 20 patients. This observation is noteworthy clinically, because delirium tremens is similar, clinically and biochemically, to Addisonian crisis, or adrenal exhaustion. The period over which recovery takes place in delirium tremens is an important consideration. A patient treated by conventional methods usually recovers in 48 to 72 hours in the absence of other complications. With corticotropin dramatic improvement was noted in three to 10 hours.

This study of a limited number of patients suggests that cortisone is effective in Korsakoff's psychosis and that corticotropin is not. Both cortisone and corticotropin are effective in the treatment of actue alcoholic intoxication. In delirium tremens corticotropin appeared to be the most effective treatment thus far.

ALPERS, Philadelphia.

CEREBRAL HEMISPHERECTOMY IN CEREBRAL PALSY. A. J. BELLER and M. STREIFLER, Harefuah **45**:219 (May 15) 1953.

Krynauw, in 1950, reported the clinical value of the removal of the affected cerebral hemisphere in spastic hemiplegia. This was confirmed by Cairns and also by Obrador. The authors report the results of hemispherectomy in a case of congenital hemiplegia with frequent epileptic seizures, mental retardation, and aggressive behavior in a 17-year-old girl. The patient had had right spastic hemiparesis since early life, an intellectual defect with irritability, and recurrent convulsive seizures since the first year of life. The left occipital lobe was ablated

in 1945; the operation did not prove helpful. Irritability became more marked, and convulsive seizures became more frequent on the right side; there was no improvement in the spastic hemiparesis. Electroencephalographic activity was diminished in both hemispheres. Pneumoencephalography early in 1952 showed no evidence of a tumor; there was widening of the whole left cerebral hemisphere. Spastic changes in the right side of the body were more pronounced than in 1945. On Jan. 30, 1952, complete left cerebral hemispherectomy was done, and that part of the hemisphere which had remained was removed in accordance with the recommendations of Krynauw. After this operation there were no convulsive seizures. Definite improvement in her mental state and in the right-sided spasticity appeared. Electroencephalographic changes became much less prominent bilaterally. The authors suggest that the remaining basal ganglia and the optic thalamus on the left side were the probable source of electrical changes.

N. Savitsky, New York.

Treatment of Multiple Sclerosis. Benjamin B. Spota and Diego Brage, Prensa méd. argent. **38**:815 (April 6) 1951.

Spota and Brage review the extensive literature on the treatment of multiple sclerosis and conclude that therapy up to the present has been ineffective. They also point out the difficulty in evaluating regimens of treatment in multiple sclerosis because of the tendency toward spontaneous improvement. The authors suggest the possibility that multiple sclerosis is a disease of adaptation. They believe this explains the accessory etiologic role of exogenous factors, such as infection and trauma. They have treated a few cases of the disease with small doses of desoxycorticosterone acetate and large doses of ascorbic acid and saw surprising results, especially when treatment was given during early stages of the illness. At present the authors are treating patients with cortisone. They believe that cortisone, and even corticotropin, should be tried in this affection, which has been so refractory to all methods of treatment up to the present time.

N. Savitsky, New York.

Contribution to the Surgery of Parkinsonism. A. Givre, Prensa méd. Argent. **39**:1238 (June 6) 1952.

Givre reports a new operative technique for treating Parkinsonism. Area 4s (strip area) of the cortex was separated from its connection to Area 6; Area 4 was resected to a depth of 1 cm. Area 4s was identified by electrical stimulation, which caused the abnormal movements to disappear. Nine patients were treated. Tremor and rigidity disappeared in eight patients, who were followed for three years. In one patient the tremor reappeared in three weeks. Motor paresis following operation cleared up in a week. An electroencephalogram obtained on the first patient after operation did not reveal any electrocortical changes. Histological examination of the resected cortex by Dr. Polak showed that these areas corresponded to Zone 4 of Brodmann. The surgical approach to Parkinsonism offers some hope to the unfortunate patients with this disease.

N. Savitsky, New York.

Peripheral Neurectomy and the Treatment of Trigeminal Neuralgia. J. Zaclis, Arq. neuro-psiquiat. **9**:228 (Sept.) 1951.

This study is based on 34 cases of trigeminal neuralgia, all treated by means of peripheral neurectomy and alcoholization of the central end of the cut nerve to retard regeneration. Twenty-three patients were followed for more than a year; 10 for more than two years, and 4 for more than three years; 6 patients could not be followed, and 1 patient up to the time of writing was free of pain. In 20 cases the neurectomy was intraorbital, and in 8, intraorbital and mental; in 3 both mental branches were cut; in 2, the frontal branch was cut, and in 1 a bilateral infraorbital neurectomy was done. In five of the cases a second operation had to be done because of recurrence of pain; in each of these cases in which there was recurrence there was freedom from pain for more than a year. The paresthesias following the operation were never severe enough to require treatment. The absence of sensation following the nerve section tended to disappear after a variable time. The disappearance of the impaired sensation is due

to the regeneration of the divided nerve and not to overlapping of surrounding nerves. After reoperation sensory changes reappeared. Facial palsy was not noted in any of the cases. One had a transitory third nerve paralysis; three became infected, and in one the skin of the face was burnt by hot compresses.

N. SAVITSKY, New York.

## Muscular System

PANCREATIC ADENOMA (HYPERINSULINISM) ASSOCIATED WITH NEUROMUSCULAR DISORDERS. R. W. BARRIS, Ann. Int. Med. **38**:124 (Jan.) 1953.

Barris reports the study of a case of progressive muscular wasting in a 42-year-old white man, in which an endocrine factor seemed responsible. There were generalized progressive wasting of muscle, muscle fasciculations, electromyographic evidence of muscle fibrillation, increased myotatic irritability, and progressive motor disability. This presumably inexorable progression of muscle atrophy was arrested after the discovery and surgical removal of a tumor of the pancreas, histologically confirmed as an islet-cell ademona.

A review of the literature shows that this is the fifth such case to be reported, all since 1946; furthermore, in four of these cases removal of a pancreatic adenoma brought about the arrest of the signs relating to progressive wasting of muscles; in the fifth case, in which a pancreatic adenoma was not discovered until autopsy, there was microscopic evidence of an associated severe and widespread degeneration of anterior horn cells of the spinal cord (amyotrophy).

The author emphasizes the probable role of endocrine dysfunction in the genesis of progressive muscular atrophy.

ALPERS, Philadelphia.

## Encephalography, Ventriculography and Roentgenography

DIAGNOSIS AND LOCALIZATION OF ORGANIC LESIONS OF THE CENTRAL NERVOUS SYSTEM USING RADIOACTIVE DIIODOFLUORESCEIN. L. DAVIS and S. I. GOLDSTEIN, Radiology **59**:514, 1952.

Davis and Goldstein report on the study of 536 cases in which radioactive diiodofluorescein was used for diagnosis and localization of suspected intracranial lesions. In 272 of the cases no surgical or postmortem evidence has been obtained to substantiate or to disprove the findings of the study with the radioactive material. In the 200 cases the diagnosis made by the authors on the basis of results with the radioactive material has been proved to be correct by surgical or postmortem study. In 64 cases the diagnosis has been proved to be incorrect or inaccurate.

Davis and Goldstein administer about 1.1 mc. of radioactive diiodofluorescein intravenously. Radioactivity at the surface of the head is at a maximum within a minute or two after the injection of the dye. It decreases rapidly for the next 10 to 30 minutes. The best time for counting is from one-half to two hours after the administration of the dye, since the decrease in radioactivity is gradual at this time. A Geiger-Mueller tube with an aluminum beta shield over the end and a lead shield at the sides is used for counting. Thirty-two different positions on the scalp are studied. Six of these are in the midline, and the other 26 are made up of 13 symmetrical positions on the two sides of the head. The tube and its shielding are positioned manually and placed at right angles to the tangent to the skull at the position being studied.

Davis and Goldstein believe that the selective deposition of the radioactive dye within tumor tissue depends mainly upon the state of the endothelium of the capillaries. The dye is localized selectively, not in the tumor tissue itself, but in its intercellular stroma, probably as a result of altered permeability of the blood vessels of the tumor. Consequently, the test is not capable of differentiating acute infections or recent hemorrhages from tumors, since there is some disturbance of capillary permeability in all these lesions. Subdural hematomas, hygromas, cysts, and aneurysms do not produce any concentration of the radioactive dye and thus are not localized by this method. The most vascular tumors concentrate the dye best, and the least vascular tumors concentrate it poorly.

The authors believe that the method is very useful in its present stage of development, both in demonstrating intracranial abnormality and in localizing the abnormality. They hope for rapid technical improvements which will make the test cheaper, simpler, and more accurate.

WEILAND, Grove City, Pa.

CONCURRENCE OF PARIETAL THINNESS WITH POSTMENOPAUSAL, SENILE, OR IDIOPATHIC OSTEOPOROSIS. B. S. EPSTEIN, Radiology **60**:29 (Jan.) 1953.

Epstein reviews the literature concerned with thinness of the parietal area and points out that very little has been written concerning this condition and its diagnosis by means of the roentgenogram. Thinning of the calvaria in the parietal region can usually be seen in a frontal projection of the skull. The Towne and the reversed Towne views are suitable for the demonstration of parietal thinning.

The author describes the x-ray findings in 26 patients for whom the diagnosis of thinning of the parietal bones had been made. Seven of the patients were referred for x-rays of the skull because of trauma to the head. Ten were referred for x-rays of the spine and skull because of backache and headache. Nine examinations of the skull were taken at Epstein's request because he had noticed evidence of osteoporosis of the thoracico lumbar portion of the spine in other examinations made on these patients. In this series of cases it was evident that parietal thinness may occur either unilaterally or bilaterally. It is often accompanied by thinning of the bone in the temporoparietal region as well. In 14 of the 19 patients for whom roentgenograms of the spine were available, definite osteoporosis of this region could be demonstrated.

Six of 10 patients for whom an x-ray of the pelvis was available showed osteoporosis in that region. Epstein is struck by the evidence that parietal thinning and osteoporosis frequently coexist, and he wonders whether they may have a common cause. He does not regard his series of cases as an index of the coincidence of the two conditions, however, in view of the selection of cases. In one-third of his reported cases x-rays of the skull were taken simply because osteoporosis was found in the spine. Probably the most widely accepted present explanation of the thinness of the parietal bones is Greig's theory that the thinness represents a dysplasia of the diploë in this region, similar to the normal condition in the lower portion of the occipital bone.

WEILAND, Grove City, Pa.

OBSERVATIONS OF PREDICTION OF FRACTURE SITE IN HEAD INJURY. E. S. GURDJIAN; J. E. WEBSTER, AND H. R. LISSNER, Radiology **60**:226 (Feb.) 1953.

The authors have written a series of articles describing the results of their study of the human skull when subjected to stress. Freshly dried human skulls are used in these studies. The internal and external surfaces are covered by the application of a strain-sensitive lacquer, which the authors call a "stress coat." Tensile stresses in the bones of the skull cause cracks to appear in the special lacquer, and the patterns assumed by the cracks in the lacquer indicate the direction of stresses in the bones of the skull.

The type of fracture depends mainly upon the velocity of the blow to the head, provided that there is adequate energy in the blow. Generally speaking, the greater the velocity of the blow, the more localized the deformity at the area of impact. High-velocity blows tend to produce perforations and depressed fractures at the site of injury.

The present study deals with low-velocity blows to the skull, in which there is enough energy to cause a skull fracture. Low-velocity blows are the ones which are usually responsible for the linear skull fractures. Gurdjian, Webster, and Lissner have divided the calvaria into 12 areas. The area of the midline of the skull is divided into midfrontal, anterior interparietal, posterior interparietal, and midoccipital. There are 4 corresponding areas on each side of the skull, making a total of 12 areas in all. The report consists of a series of diagrams showing the main locations of linear fractures which result from low-velocity blows to each of these 12 areas of the skull. The common course that the fracture lines assume are diagrammed, and the percentage of occurrence for each site of the fracture line is presented. Thus, a low-velocity blow in the left frontal area produces a vertical fracture in the left temporal area in 52% of cases. A fracture through the roof of the left orbit occurs 35% of the time.

Five other, less common, fractures resulting from such a blow are described. A study of the original article is necessary to appreciate the presentation, which is mainly diagrammatic.

WEILAND, Grove City, Pa.

THE ROENTGEN FINDINGS IN NEUROBLASTOMA. R. S. SHERMAN and R. LEAMING, Radiology **60**:837 (June) 1953.

Sherman and Leaming state that the diagnosis of neuroblastoma should be considered in the case of an infant or a young child with evidence of an abdominal mass, adenopathy, a tumor of the eye or the orbit, or bilateral involvement of bones. Well-developed evidences of neuroblastoma are pathognomonic in roentgenograms of the skull. A soft-tissue mass in the region of an adrenal gland which contains calcification and presents indistinct margins in a roentgenogram of the abdomen is also an extremely reliable sign. Of equal reliability is the presence of bilateral symmetrical areas of bone destruction, showing poorly defined borders, destruction of cortex, and periosteal reaction. These lesions have a fine, patchy internal pattern, are located oftenest in the femora and humeri, and progress rapidly. The bone lesions have a tendency to produce soft-tissue masses, and they give evidence of response to x-ray treatment. The roentgenographic diagnosis of neuroblastoma depends on the changes listed above, particularly upon combinations of these changes. Most patients with neuroblastoma present two or all of the changes described.

WEILAND, Grove City, Pa.

## Congenital Anomalies

MICROPHTHALMOS AND DEFORMITY OF THE EXTREMITIES. PAOLLO RIZZO, Riv. oto-neuro-oftal. **26**:327 (July-Aug.) 1951.

A 22-year-old single woman showed mild microphthalmos, syndactyly of the second and third toes of both feet, right internal strabismus, and decreased size of the left side of the face and the left upper limb. The fingers of the hands were small and of equal size. There were frontal hyperostosis, dextroscoliosis of the mid-dorsal region, and levoscoliosis of the lumbar region. There was a mild valgus deformity in the elbow regions. In the lower limbs, there were enlargement of the anterior part of the feet and microdactyly and isodactyly of the last four toes. The author considers this case one of a variant of Biemond's syndrome (polydactyly, mental retardation, infantilism, and hypophysial obesity). The defects are considered congenital malformations on a dysgenetic basis.

N. SAVITSKY, New York.

# News and Comment

## THE AMERICAN NEUROLOGICAL ASSOCIATION

The Seventy-Ninth Annual Meeting of the American Neurological Association will be held at the Hotel Claridge, Atlantic City, N. J., from June 14-16, 1954.

## AMERICAN PSYCHOSOMATIC SOCIETY

At the annual business meeting of the American Psychosomatic Society, held on March 27, 1954, the following persons took office: Lawrence S. Kubie, M.D., president; Stanley Cobb, M.D., president-elect; Theodore Lidz, M.D., secretary-treasurer.

Elected to council positions were Dane G. Prugh, M.D.; David Shakow, Ph.D.; Stewart Wolf, M.D.

The Twelfth Annual Meeting of the American Psychosomatic Society will be held on May 4 and 5, 1955, at the Claridge Hotel in Atlantic City, N. J.

## FIFTH INTERNATIONAL CONGRESS ON MENTAL HEALTH AND THE INTERNATIONAL INSTITUTE ON CHILD PSYCHIATRY

The Fifth International Congress on Mental Health will meet at the University of Toronto, Aug. 14 to 21, 1954. The theme is Mental Health in Public Affairs. There will be technical sessions each morning organized around five major topics: Areas of Partnership in Mental Health and Public Health; Mental Health in Governmental Activities; Mental Health of Children and Youth; Community Partnership in Mental Health; Professional Advances in the Mental Health Field.

In addition to the technical sessions, there will be round table discussions designed to meet the interests of special groups of delegates on the following topics: Mental Health and Education; Parent Education; The Role of the Volunteer in Mental Health Work.

The International Institute on Child Psychiatry will meet on Aug. 13 and 14. The theme of the Institute is The Emotional Problems of Children Under Six.

On Friday, Aug. 13, small working groups will spend the entire day in discussing prepared clinical case studies. On Saturday morning, Aug. 14, larger group meetings will consider research reports.

The case studies and research reports are classified in four major areas: Psychoses in Children; Prevention; Interrelationship of Physical and Emotional Factors; Maternal Separation. Institute registrants will be asked to select the area in which they are most interested. In so far as possible, assignment to group and section meetings will be made in accordance with their choice.

On Saturday afternoon, there will be a plenary session, with papers presented by Dr. Georges Heuyer, France; Dr. Emanuel Miller, United Kingdom; Dr. Benjamin Spock, United States of America.

The inclusive fee for both conferences is $25, $20 if paid before June 1st. All fees and inquiries should be sent to the Executive Officer, Fifth International Congress on Mental Health, 111 St. George St., Toronto, Canada.

## AMERICAN ELECTROENCEPHALOGRAPHIC SOCIETY MEETING

The eighth annual meeting of the American Electroencephalographic Society will take place at the Hotel Claridge, Atlantic City, N. J., on June 11, 12, and 13, immediately preceding the annual meeting of the American Neurological Association. The scientific sessions will start on Friday afternoon, June 11.

A symposium on The Rhinencephalon (Its Relationship to Both Clinical Electroencephalography and Experimental Neurophysiology with Special Reference to Its Electrical Activity in Relation to Behavior and Symptoms), under the chairmanship of Dr. Robert Schwab, will be held on Sunday, June 13, from 9:00 a.m. until 1:00 p.m.

There will be a special session on Medico-Legal Aspects of Clinical Electroencephalography on Friday, June 11, from 8:00 p.m. until 10:00 p.m. The moderator will be Dr. A. Earl Walker.

The annual banquet will take place Saturday, June 12, at 8:00 p. m. Business sessions will take place Friday, June 11, from 4:00 p.m. to 6:00 p.m. and from 10:00 p.m. to 12:00 p.m.

Committee and council meetings will be held all day Thursday, June 10, and Friday, June 11, from 9:00 a.m. until 12:00 M. The registration desk will be open on Friday, June 11, at 9:30 a.m.

# Books

**Human Behavior in the Concentration Camp.** By Dr. Elie A. Cohen. Price, $5.00. Pp. 295. W. W. Norton & Company, Inc., 101 Fifth Avenue, New York 3, 1953.

It is remarkable how quickly the public has formed a distaste for books about the German concentration camps. Of course, one of the first and most thorough descriptions of what really occurred in these hell-holes was in the volumes issued by the United States Government Printing Office, entitled "Trial of the Major War Criminals Before the International Military Tribunal. Nurenberg, Nov. 14, 1945-Oct. 1, 1946." These papers grew to a dozen volumes, thousands of pages crammed with cold prison records, captured German directives, retrieved secret documents, and thousands of pages of the testimony of the German politicians, military men, and underlings. Through it all, the reader got the nauseating realization that each sadistic officer or politician blamed his actions on orders from higher up and complained that he was merely carrying out his duty. Yet, through it all, there were innumerable instances where new perverted, sadistic, and degrading practices were invented all down the line of command. A few other books were published from time to time describing the horrors of these camps. When the Russian films of Maidenek and the American movies of Auschwitz were exhibited to the American public, this reviewer noted the bated breath and quiet, almost unbelievable horror of the audiences when they were shown, at last, the fantastic scenes of these abattoirs. You could almost smell the stench.

Then came the book, "Five Chimneys," by Olga Lengyel. It had a moderate success. It, too, was published in 1947. Since then fewer publications of books on this subject are appearing. The languid interest of the public operates in favor of the law of diminishing returns, and publishers shy away. Now Dr. Elie Cohen, a Dutch physician, who was at Auschwitz for more than three years, has published his impression of the effects of the concentration camps on the personality changes of the prisoners and also has told what the concentration camp did to the Nazi jailers.

It is remarkable that this prisoner has managed to avoid emotional involvement in this psychological study. There is a hint that his emotional detachment is, in itself, a product in the depersonalization which he so accurately describes in this book.

Throughout his account of the medical experiments, such as the freezing of the prisoners, the injection of germs of typhus and tuberculosis, he manages, despite the fact that he was a victim, to be dispassionate and coldly accurate. The testing of dubious drugs on prisoners is a revealing chapter on the intimate relationship between the directors of the I. G. Farben Industrie and the depraved medical officers of the German S.S. (*Schutzstaffel*). The involvement of the German people in these atrocities he ascribes to their education. The fact that they had been constantly, for a decade, told that the Poles, the gypsies, and the Jews were guilty and inferior made them willing to act sadistically and made the population, who *knew* about the concentration camps, indifferent to the fate of their countrymen.

Altogether an exceedingly good book, well printed, well bound, with a good bibliography, and completely annotated.

**Principles of Neurology in the Light of History and Their Present Use.** (Nervous and Mental Disease Monograph 80.) By Walther Riese. Price, $6.00. Pp. 177. Nervous and Mental Disease Monographs, 70 Pine St., New York 5, 1950.

This is a belated review of a stimulating and instructive monograph dealing with the basic concepts of function within the nervous system. It defines and elaborates the various theories of nervous system action in health and disease and leans heavily on the principles elucidated by Hughlings Jackson. It is concerned with a discussion of integrative action and correlated

problems, such as inhibition and resistance; with the evolution of nervous function, dissolution, and cerebral dominance; the equipotentiality of nervous structures; the problems of cerebral localization, and the mechanism of reactions, such as restitution and substitution of function following disease of the brain. These are but a few of the problems with which the author deals. His range is wide, but his style is extremely condensed; and the monograph, though extremely rewarding, requires careful reading.

It is possible only to comment on scattered areas within the monograph. According to Jackson all functions of the nervous system and their changes under pathological conditions are expressed in terms of excitation (or sensory function) and reaction (or motor function), the element of consciousness being deliberately ignored. By this means the number of basic symptoms is reduced "and the various diseases of the central nervous system can be accounted for by combinations of these symptoms and their genesis according to the regions involved." By the combination of innumerable basic coordinating mechanisms the function of each of them necessarily undergoes modification, the behavior of a living unit when isolated being different from its behavior as a part of a group. In the latter instance each of the constituent parts undergoes influence by the rest. "This influence has been expressed in terms of a hierarchy of nervous function" (Jackson). According to this doctrine, the lowest and middle levels of the central nervous system are under the dominating influence of the higher ones. Riese states that this hierarchy of nervous function is not to be "conceived as a fixed and rigid one-way dominance exerted by the higher levels, but rather as a mobile control exerted by one level over the others, according to circumstances and susceptible of being reversed under new conditions."

Riese casts some doubt on the principle of cerebral dominance and asserts that "any lesion disturbing cerebral mechanisms must be interpreted in the light of time." He states further that "nothing seems indeed to be more difficult than to resist the temptation of thinking and speaking in terms of a doctrine of localization of functions, although the facts available admit only of localization of symptoms." Of cerebral dominance he says that "any lesion within 'the critical areas of language' disturbs the speech mechanism in a different way, according to the site of the damage. But this does not imply that those parts are at the same time the 'major' or the 'leading' ones in an intact system." The issue may be one not of dominance but of vulnerability. "The question is not whether the left hemisphere is more vulnerable in a right-handed individual, but whether the mechanism of speech is more easily disturbed by lesions involving the left than by those involving the right hemisphere."

It is impossible to review in detail the many problems discussed by Riese. There are excellent discussions on the problems of compensation and localization, not only of the Jackson but of the chronogenetic localization concept of von Monakow, the basic element in which is seen in the fact that each nervous function is the result of a historical evolution. There is available in this monograph also a good discussion of the principle of diaschisis (von Monakow), one of the few available in English.

This monograph is extremely stimulating. The problems with which it deals are those with which all neurologists are vitally concerned. It is recommended without reserve.

**Visceral Innervation and Its Relation to Personality.** By Albert Kuntz. Publication No. 115, American Lecture Series, monographs in American Lectures on Anatomy, edited by Otto F. Kampmeier. Price, $4.50. Pp. 160. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1951.

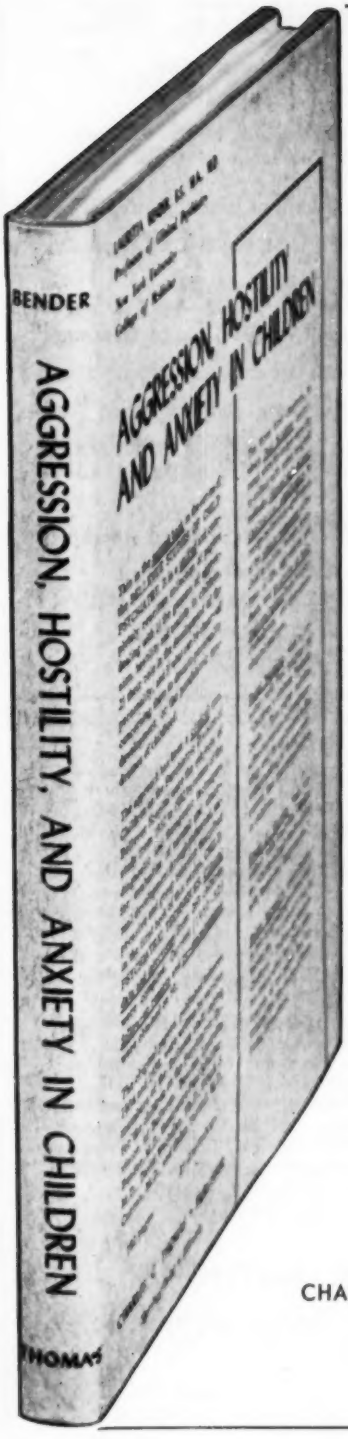
Chapters 1, 2, 3, and 5 contain a lucid and well-written account of the anatomy of the autonomic nervous system. Chapter 4, entitled General Physiology, opens with a brief and inadequate account of the chemical mediation of nerve impulses (for example, no mention is made of the existence of adrenoxidases or cholinesterases) and continues with a subsection on endocrine influences in visceral functions, which is equally inadequate. Homeostasis is sketchily disposed of, and the roles of the visceral integrating centers in temperature regulation, metabolism, and sleep are briefly summarized.

A surprising transition in content is made between the analysis of the pupillary reflex, which closes Chapter 5, and the definition of personality, which opens Chapter 6. This section deals with the latter half of the title, namely, the relation of the autonomic nervous system

to personality. Having demonstrated the anatomical interconnections of visceral innervation with the somatic, sensory, and cortical systems, the author concludes that abnormal emotional states result from visceral dysfunction, the latter being due to autonomic imbalance. Autonomic imbalance, apparently, may be either a constitutional steady-state phenomenon, which determines a person's behavior in society, or a momentary state of dysequilibrium, which may become self-perpetuating through a mechanism of continuous feed-back. The author seems to feel that all this is rather dangerous and states the belief (page 135):

"In all of this the viscera play a major role, but they must be controlled by the brain, not the brain by the viscera. When the viscera are in control, certain emotions produce disastrous results. When the brain is in control, such emotions are held in check and may be completely suppressed. Passion may be mastered by intelligence and determination." The amazing part of the whole thing is that Pelagius reached practically the same conclusions 1,500 years ago, without the benefit of a knowledge of the neuron paths of the autonomic nervous system.

The writing in the last chapter is loosely done; such terms as emotion, feeling, passion, emotional experience, emotional expression, emotional awareness, emotional situations, simple emotions, and pleasurable emotions are abruptly introduced with apparently no regard for any semantic difficulties which might arise. The style is pedagogic throughout, and, while welcome in explaining the intricacies of visceral innervation, it is curiously out of place in the science of human relationships.

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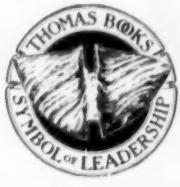

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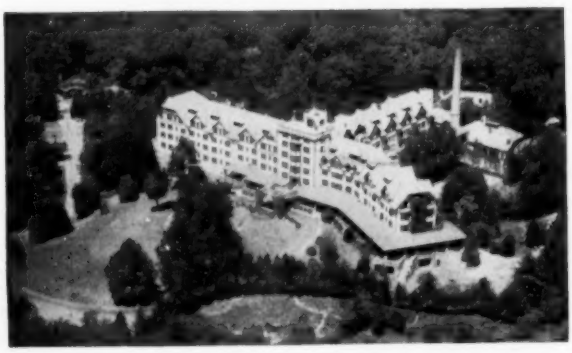
*Medical Director and Superintendent*

# Appalachian Hall



*An institution for rest, convalescence, the diagnosis and treatment of nervous and mental disorders, alcohol and drug habituation.*

Appalachian Hall is located in Asheville, North Carolina. Asheville justly claims an unexcelled all year round climate for health and comfort. All natural curative agents are used, such as physiotherapy, occupational therapy, shock therapy, outdoor sports, horseback riding, etc. Five beautiful golf courses are available to patients. Ample facilities for classification of patients. Room single or en suite with every comfort and convenience.

*For rates and further information, write*

APPALACHIAN HALL
Asheville, North Carolina

**M. A. Griffin, M.D.**
**Wm. Ray Griffin, M.D.**